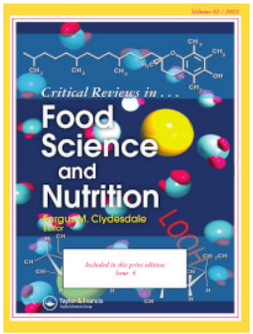

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REVIEW

Nobiletin as a chemopreventive natural product against cancer, a comprehensive review

Yun-Yi Chen[a], Jiao-Jiao Liang[a], Deng-Liang Wang[b], Jie-Biao Chen[a], Jin-Ping Cao[a], Yue Wang[a] and Chong-De Sun[a]

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ABSTRACT

As a leading cause of death, second only to heart disease, cancer has always been one of the burning topics in medical research. When targeting multiple signal pathways in tumorigenesis chemoprevention, using natural or synthetic anti-cancer drugs is a vital strategy to reduce cancer damage. However, toxic effects, multidrug resistance (MDR) as well as cancer stem cells (CSCs) all prominently limited the clinical application of conventional anticancer drugs. With low side effects, strong biological activity, unique mechanism, and wide range of targets, natural products derived from plants are considered significant sources for new drug development. Nobiletin is one of the most attractive compounds, a unique flavonoid primarily isolated from the peel of citrus fruits. Numerous studies in vitro and in vivo have suggested that nobiletin and its derivatives possess the eminent potential to become effective cancer chemoprevention agents through various cellular and molecular levels. This article aims to comprehensively review the anticancer efficacy and specific mechanisms of nobiletin, enhancing our understanding of its chemoprevention properties and providing the latest research findings. At the end of this review, we also give some discussion and future perspectives regarding the challenges and opportunities in nobiletin efficient exploitation.

KEYWORDS

Cancer; chemoprevention; mechanism; nobiletin

Introduction

Cancer, also known as malignant tumor, has the typical hallmarks of sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, as well as activating invasion and metastasis (Hanahan and Weinberg 2000). With the advancement of technology and the deepening of research, cancer's biological characteristics have become more explicit and complete (Hanahan and Weinberg 2011; Senga and Grose 2021), so are the physical traits (Nia, Munn, and Jain 2020). Cancer is considered an evolving, dynamic, heterogeneous system (Floor et al. 2012). The occurrence and development of cancer is a multi-factor, multi-step complex process closely related to genetic factors, bad living habits, occupational exposure and environmental pollution (Liu and Dong 2021). Elusive features establish cancer as the second leading cause of death in the world. According to the latest global cancer report released by the International Agency for Research on Cancer (IARC), there were 19.29 million new cancer cases and 9.96 million cancer deaths worldwide in 2020, with a mortality rate of 51.8% (Sung et al. 2021). Notably, as the most populous country in the world, lung cancer has become the top killer of cancer-related deaths in China (Sun et al. 2020).

Chemotherapy, radiotherapy, together with surgical resection are the most effective and extensive approaches for cancer management (Fischer, Seo, and Efferth 2018; Zhang et al. 2018). However, all these traditional treatments would seriously reduce patients' quality of life and would cause nausea, vomiting, fever, skin damage, hair loss, fatigue, and other side effects. Toxic effects, multidrug resistance (MDR), and the existence of cancer stem cells (CSCs) also seriously limited the clinical application of traditional anticancer agents (Catanzaro et al. 2018; Zhang, Feng, and Kennedy 2017a). At present, no impeccable therapy for malignancies has yet been found. Therefore, the prevention of cancer progression has become an important strategy to eliminate the harm caused by cancer. Cancer chemoprevention refers to the use of multiple intervention strategies through natural or synthetic drugs to reverse, inhibit or prevent the progress of carcinogenic processes at different stages (Kaur et al. 2018). Great progression has been achieved in the field of chemoprevention through the study of individual compounds, most of which were either natural in foods or synthetic derivatives of these food compounds (Stoner 2020). Natural products represent an incredible treasure trove of bioactive molecules, so the inclusion of targeted supplements of natural products in the diet is considered a healthy lifestyle as well as an integral part of cancer chemoprevention.

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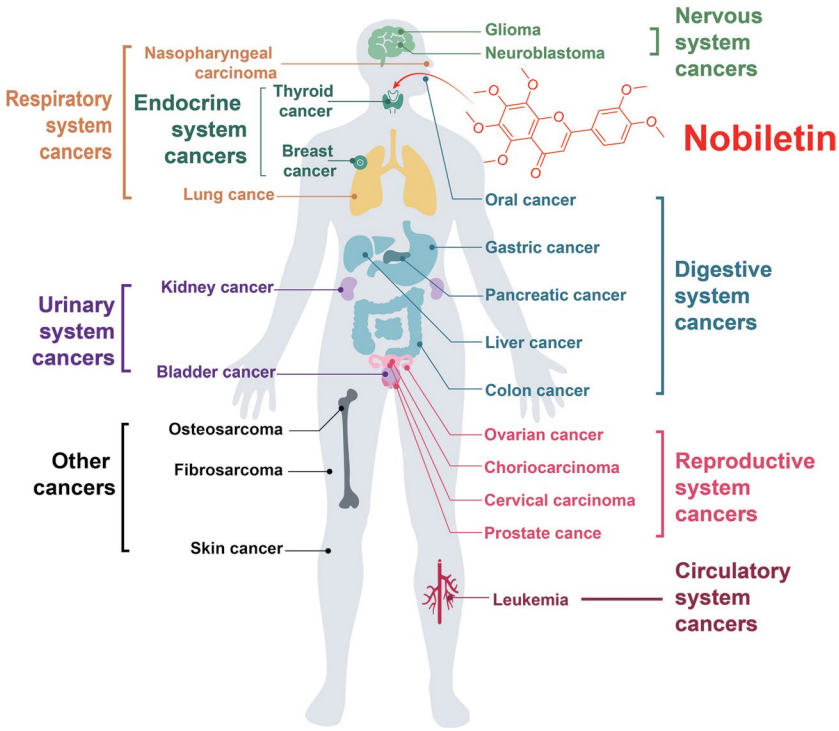

Figure 1. Reported anticancer activity of nobiletin.

Moreover, due to the advantages of low side effects, strong biological activity, unique mechanism of action and a wide range of targets, natural products and their derivatives, especially phytochemicals, have powerfully attracted the attention of researchers and become an essential source of new drug research and development in the field of cancer treatment (Atanasov et al. 2021; Newman and Cragg 2020).

Flavonoids are a unique class of bioactive substances in natural polyphenols, which are rich in plant-based foods, such as vegetables, fruits, grains and tea, as well as most medicinal plants (George, Dellaire, and Rupasinghe 2017). *Citrus* species have always received extensive attention in the field of biofunctional components development, which is inseparable from their rich flavonoids (Denaro et al. 2020). To date, more than 10000 flavonoids have been identified and can be subdivided into flavones, isoflavones, flavanones, flavonols, anthocyanidins and flavans (Ponte et al. 2021). It is generally believed that flavonoids are synthesized by the phenylpropanoid pathway and modified by hydroxylase, methoxy transferase, and glycoside transferase at multiple sites to form diverse flavonoids (Le Roy et al. 2016). Structural diversity gives them a wide range of biological activities, including anti-viral, anti-inflammatory, cardioprotective, anti-diabetic, anti-cancer, anti-aging properties and so on (Wang, Li, and Bi 2018b).

Nobiletin (NOB) is one of the most well-studied compounds in polymethoxylated flavonoids (PMFs) with the specificity of variety and tissue distribution. It mainly exists in mandarin, tangerine, orange and some hybrid oranges, and only in the flavedo of the fruit (Wang et al. 2021b). NOB has been proved to be a multi-functional pharmaceutical agent beneficial to various human systems (Huang et al. 2016), with anti-cancer (Ashrafizadeh et al. 2020), anti-inflammatory (Wang et al. 2021a), anti-oxidation (Zhang et al. 2019), anti-diabetes (Nguyen-Ngo et al. 2020), cardiovascular protection (Yang et al. 2019), neuroprotection (Matsuzaki and Ohizumi 2021), regulating circadian rhythm (Gloston, Yoo, and Chen 2017) and other bioactivities. Among these, anti-cancer has received the most attention. And a large number of reports have demonstrated that NOB has the potential of inhibiting the occurrence and development of cancer, such as inhibiting cancer cell proliferation, promoting apoptosis, inducing cell cycle arrest, regulating autophagy, inhibiting invasion and relieving drug resistance and so on. However, opinions vary widely on the anticancer efficacy and mechanism of NOB. In this article, we try to comprehensively review the anticancer potential and chemoprevention mechanism of NOB in hopes of showing the anticancer properties of NOB in vivo and in vitro as well as the latest achievements. Finally, based on the challenges of bioavailability and safety faced by NOB, we also discuss some of the open questions and future perspectives about the effective utilization of NOB in cancer prevention and treatment.

Potential role of nobiletin in cancer therapy

NOB is a typical methoxyflavone that is flavone substituted by methoxy groups at positions 5, 6, 7, 8, 3′ and 4′ respectively (Huang et al. 2016; Itoh, Iwata, and Toda 2016). As one of the most potent flavonoids, NOB has been confirmed to exhibit preventive and therapeutic effects on a series of malignant tumors (Figure 1). In other words, NOB establishes a whole-body defense barrier for living organisms and plays an essential role in resisting the invasion and spread

Table 1. Cell lines and animal strains commonly used in the study of the activity of nobiletin.

Cancer	In vitro	In vivo
Bladder cancer	BFTC cells	/
Bowel cancer	/	$Apc^{Min/+}$ Mice, F344 rats
Brain tumor	IPMA-E, IPSF-PA, IPSH-OA2, IPAB-AO3, IPMC-A3, IPLC-GM, AMHFB-GM	male Wistar rats
Breast cancer	TNBC cell lines: Hs578T, $Hs578Ts(i)_8$, MDA-MB-231, MDA-MB-468 ER^+cell lines: MCF-7, T47D Her^{2+}cell lines: SK-BR-3, MDA-MB-435 Normal cell lines: MCF10A	C57Bl/6 mice, female Sprague Dawley rats
Cervical caicinoma	HeLa cells	/
Choriocarcinoma	BeWo cells	/
Colon cancer	HCT116, HT29, Colo320, SW480, Caco-2, Colo205, Colo320DM, LS174T, LS180	male C57BL/KsJ-db/db mice, male Crj: CD-1 (ICR) mice Sprague-Dawley rats, F344 rats
Fibrosarcoma	HT-1080	
Gastric cancer	TMK-1, MKN-45, MKN-74, KATO-III, TGBC11TKB, St-4, AGS, SNU-1, SNU-16, GES-1, NCI-N87, Hs738St./Int	severe combined immuno-deficient (SCID) mice
Glioma	IPMA-E, IPSF-PA, IPSH-OA2, IPMC-A3, AMHFB-GM, C6 Glioma cells, U87, U251, U43, Hs683	
Kidney cancer	ACHN, Caki-2, 786-O	male nude mice, C57 mice
Leukemia	CCRF-HSB-2, MOLT-4, MOLT-4/DNR cells, K562, K562/ADM, WEH13B (JCS), KHYG-1 (NK), THP-1, U-937, HL-60, HEL 92.1.7, OCI-AML3, MV4-11, PBMCs, RAW 264.7	inbred male BALB/c mice, ICR mice
Liver cancer	HuH-7, HepG2, MH1C1, SMMC-7721, H22, Hep3B, FL83B	F344 rats, Kunming (KM) male mice
Lung cancer	A549, A549/ADR, A549/T, HCT8/T, H460, H1299, H441	female A/J mice, Balb/c-nude mice, male Wistar rats, male Sprague-Dawley
Melanoma	B16 mouse melanoma cells, B16 melanoma 4A5, B16/F10 melanoma cells, HM3KO	/
Nasopharyngeal carcinoma	C666-1, HONE-1, NPC-BM	male BALB/c nude mice
Neuroblastoma	SK-N-SH, SH-SY5Y	/
Oral cancer	Human OSCC cell lines: Ca9-22, HSC-3, TSC-15, TCA-8113 and CAL-27 primary normal human oral epithelial cells (H0ECs)	female Syrian golden hamsters (Lak:L VG)
Osteosarcoma	Human osteogenic sarcoma: U2OS, HOS Mouse osteoblast: MC3T3-E1	/
Ovarian cancer	OVCAR-3, A2780/CP70, A2780/T, CaoV3, ES-2, HO-8910, SKOV3, SKOV3/TAX, IOSE-364 (normal)	chicken embryo chorioallantoic membrane (CAM), male nude mice
Pancreatic cancer	MIA-PaCa-2, ms-1 cells (normal)	/
Prostate cancer	PC-3 (hormone-independent), LNCaP (hormone-dependent), DU145, RWPE-1 (normal)	TRAP rats (SD* wild-type)
Skin cancer	HL60, RAW 264.7	specific pathogen-free female (SPF) SENCAR mice, female ICR mice
Squamous cell carcinoma	HTB43, TCA-8113, CAL-27	/
Thyroid cancer	Human cell lines of anaplastic thyroid carcinoma (ATC): T235, T238 Rat normal thyroid cells: PCCL3	/

of adverse factors. Up to now, researchers have carried out extensive and in-depth studies on the therapeutic effects of NOB in different types of cancer, among which breast cancer (Zhang et al. 2020a), lung cancer (Sun et al. 2019), colon cancer (Goh et al. 2019) and leukemia (Yen et al. 2020) have attracted the most attention due to their high incidence and refractory. The cell lines and animal models commonly used by investigators in in vivo and in vitro studies of various types of cancers are shown in Table 1.

It is worth noting that the sensitivity to NOB varies considerably across different cancer types, which partly explains the various cure validity of NOB in diverse cancers (Table 2). In other words, NOB has a preference for specific tumor cells. This anticancer specificity is most likely to be derived from the differences of the mechanism described later and is closely associated with tissue type, metabolic pathway, etc.

Not only that, NOB combined with a variety of chemotherapy agents has been shown to have a significant synergistic effect (Guney Eskiler et al. 2019; Sousa et al. 2020; Wu et al. 2017b). More importantly, it can reverse MDR and improve the effectiveness of cancer chemotherapy (Feng et al. 2020; Moon et al. 2018). Moreover, the derivatives and metabolites of NOB also have excellent chemoprevention effects (Huang et al. 2016; Sun et al. 2019). Growing evidence indicates that NOB metabolites show more potent anticancer benefits than their parent compounds, such as 5-demethylnobiletin (5-DMN) and 4′-demethylnobiletin (4′-DMN) (Song et al. 2016; Wu et al. 2018). And some scholars believe that the anticancer effect of NOB may be largely dependent on its metabolites (Goh et al. 2019). However, there are few clinical trials on the anticancer activity of NOB, which need to be further explored.

Mechanism of nobiletin's chemopreventive activity

Apoptosis induction

Apoptosis is a form of programmed cell death regulated by multiple signal transduction pathways. It is an internal controllable mechanism of cells initiated under physiological or pathological regulation. Three phases can be discerned in apoptosis: induction phase, execution phase and effect phase (Krueger et al. 2001). Apoptosis induction mainly includes the extrinsic (mitochondrial and endoplasmic reticulum)

Table 2. Cytotoxicity of nobiletin in different cancer cell lines.

Cancer type	Cell line	Concentration	Activity	Assay (Treatment duration)	Reference
Bladder cancer	BFTC cells	60, 80 and 100 μM	42%, 62% and 80% growth inhibition	MTT assay (24 h)	Goan et al. (2019)
Brain cancer	IPMC-A3	10 ng/ml ~ 10 μg/ml	IC_{50} = 4 μg/ml	MTT assay (24 h)	Rooprai et al. (2001)
Breast cancer	Hs578T	100 μM	30% growth inhibition	MTT assay (24 h)	Borah et al. (2017)
	$Hs578Ts(i)_8$				
	MDA-MB-231	0 ~ 200 μM	IC_{50} = 200 μM	MTT assay (24 h)	Baek et al. (2012)
	MCF-7	0 ~ 100 μM	IC_{50} = 86.9 μM	MTT assay (24 h)	Chen et al. (2014a)
	SK-BR-3		IC_{50} = 69.6 μM		
	MDA-MB-231		IC_{50} = 59.3 μM		
	MCF-7	0.01 ~ 100 μM	IC_{50} = 40 μM	MTT assay (96 h)	Surichan et al. (2012)
	MCF-7	100 μM	15%, 25% and 35% growth inhibition	MTT assay (24 h, 48 h and 72 h)	Rahideh et al. (2017b)
	MDA-MB-468	0.001 ~ 100 μM	IC_{50} = 0.1 ± 0.04 μM	MTT assay (24 h)	Surichan et al. (2018)
	MCF-7	0 ~ 300 μM	IC_{50} = 200 μM	MTT assay (24 h)	Sp et al. (2017)
	T47D				
	MCF-7	12.5, 25, 50, 100, 200 μM	14.7%, 20.7%, 28.8%, 39.7% and 45.6% growth inhibition	MTT assay (24 h)	Liu et al. (2018b)
	MCF-7	60 μM	50% ~ 70% growth inhibition	Beckman Coulter Z1 particle counter (12-96 h)	Morley, Ferguson, and Koropatnick (2007)
	HT-29				
	MDA-MB-435	100 μM			
Cervical caicinoma	HeLa	50 ~ 200 μg/ml	IC_{50} = 56.54 μM	MTT assay (72 h)	Kim et al. (2010)
	HeLa	0.0061 ~ 100 μM	IC_{50} = 46.185 μM	CCK-8 assay (48 h)	Nguyen et al. (2017)
Choriocarcinoma	BeWo	10, 33, 100 μM	Non ~ toxic	CCK-8 assay (72 h)	Zhang et al. (2020b)
Colon cancer	HCT116, HT29	50 μM	~ 50% growth inhibition	MTT assay (72 h)	Wu et al. (2015)
		2.03 μM	Non ~ toxic	MTT assay (96 h)	
	colo320	0 ~ 300 μM	IC_{50} = 40.4 ± 9.1 μM	MTS assay (48 h)	Zheng et al. (2002)
	sw480		IC_{50} = 245 ± 9.1 μM		
	caco-2		IC_{50} = 305.6 ± 41.9 μM		
	HCT116	10 ~ 50 μM	IC_{50} = 37 μM	MTT assay (48 h)	Qiu et al. (2010)
	HT29		IC_{50} = 46.2 μM		
Fibrosarcoma	HT-1080	64 μM	52% inhibition of invasive activity	tumor Invasion Assay (24 h)	Sato et al. (2002)
Gastric cancer	TMK-1	0 ~ 200 μM	IC_{50} = 134.8 μM	MTT assay (48 h)	Yoshimizu et al. (2004)
	MKN-45		IC_{50} = 226.3 μM		
	MKN-74		IC_{50} = 189.7 μM		
	KATO-III		IC_{50} = 146.3 μM		
	TGBC11TKB	8.3 μM	IC_{50} = 8.3 μM	Alamar blue assay (3d)	Kawaii et al. (1999)
	TMK-1	0 ~ 256 μM	LC_{50} = 156 μM	MTT assay (48 h)	Minagawa et al. (2001)
	MKN-45		LC_{50} = 494 μM		
	St-4		LC_{50} = 655 μM		
	SNU-16	50 μM	58.35% growth inhibition	MTT assay (48 h)	Moon et al. (2013)
	GES-1	80 μM	60% growth inhibition	MTT assay (24 h)	Ouyang, Li, and Ling (2020)
	NCI-N87	0 ~ 100 μM	IC_{50} = 18.8 LC_{50}>100	MTT assay (48 h)	Sekiguchi, Washida, and Murakami (2008)
Glioma	C6	10 ~ 100 μM	IC_{50} = 30 μM	MTT assay (24 h)	Aoki et al. (2013)
	U87, U251	20 μM	20% growth inhibition	CCK-8 assay (24 h)	Zhang et al. (2017b)
	U87	50 and 100 μM	24.5 ± 5.8% and 49.2 ± 3.4% growth inhibition	MTT assay (24 h)	Lien et al. (2016)
Kidney cancer	ACHN	80 μM	16.94% and 32.64% growth inhibition	CCK-8 assay (48 h)	Wei et al. (2019)
	Caki-2				
	Caki-1	50 μM	20% growth inhibition	CCK-8 assay (24 h)	Liu et al. (2018a)
	786-O	12.5 ~ 25 μM	Non ~ toxic		
Leukemia	CCRF-HSB-2	13.0 μM	IC_{50}	Alamar blue assay (3d)	Kawaii et al. (1999)
	MOLT-4	0.001 ~ 100 μM	IC_{50} = 12.6 μM	[^{3}H] thymidine incorporation	Ishii et al. (2010)
	THP-1	20 ~ 100 μM	IC_{50} = 54.8 μM	MTT assay (48 h)	Chen et al. (2018)
	U-937		IC_{50} = 45.2 μM		
	HL-60		IC_{50} = 45.8 μM		
	K562	10 ~ 100 μM	IC_{50} = 82.49 μM	MTT assay (48 h)	Yen et al. (2020)
	U937, THP-1, CIAML3, MV4-11	0 ~ 160 μM	IC_{50} = 40 ~ 80 μM	MTS assay (24 h)	Hsiao et al. (2014)
	HL-60		IC_{50} <40 μM		
	HL-60	40, 80 μM	15%, 30% growth inhibition	MTT assay (12 h)	Lee et al. (2002)
Liver cancer	HuH-7	100 μM	30% growth inhibition	Alamar blue assay (24 h)	Nemoto et al. (2013)
	HepG2	10^{-6} ~ 10^{-2} M	EC_{20} = 10^{-3} M	WST-1 assay (72 h)	Ohnishi et al. (2004)
	SMMC-7721	2 ~ 128 mg/L	IC_{50} = 26.51 mg/L	MTT assay (48 h)	Ma et al. (2014)
	HepG2	0 ~ 25 μM	IC_{50} = 10 μM	MTT assay (24 h)	Shi et al. (2013)
	HepG2	6.25 ~ 100 μM	IC_{30} = 30.61 μM	crystal violet assay (24 h)	Yousef et al. (2020)
	Huh-7		IC_{30} = 43.56 μM		

Table 2. (Continued).

Cancer type	Cell line	Concentration	Activity	Assay (Treatment duration)	Reference
Lung cancer	A549	22.0 μM	IC_{50} = 22.0 μM	Alamar blue assay (3d)	Kawaii et al. (1999)
	A549	1.25 ~ 80 μg/ml	IC_{50} = 23.82 ± 5.15 μg/ml	MTT assay (48 h)	Luo, Guan, and Zhou (2008)
	H460	10 ~ 50 μM	IC_{50} = 78.44 μM	MTT assay (72 h)	Sun et al. (2019)
	H1299		IC_{50} = 54.33 μM		
	A549	50 μM	25% growth inhibition	MTT assay (48 h)	Moon et al. (2018)
	H1299	100 μM	30% growth inhibition	MTT assay (24 h)	Gao et al. (2015)
	A549, H1229	0 ~ 100 μM	IC_{50} = 10 μM	MTT assay (24 h)	Da et al. (2016)
Melanoma	B16-melanoma 4A5	18.0 μM	IC_{50} = 18.0 μM	Alamar blue assay (3d)	Kawaii et al. (1999)
	HM3KO	10 μg/ml	10% growth inhibition	MTT assay (120 h)	Yoshizaki, Hashizume, and Masaki (2017)
	B16-melanoma 4A5	0 ~ 250 μM	IC_{50} = 88.6 μM	MTT assay (72 h)	Zhang et al. (2007)
Nasopharyngeal carcinoma	C666-1	0 ~ 100 μM	IC_{50} = 5 μM	CCK-8 assay (48 h)	Zheng et al. (2019)
	HONE-1, NPC-BM	0 ~ 40 μM	Non ~ toxic	MTT assay (24 h, 48 h and 72 h)	Chien et al. (2015)
Neuroblastoma	SK-N-SH	100 μM	30% growth inhibition	Alamar blue assay (24 h)	Nemoto et al. (2013)
	SH-SY5Y	30 μM	15.4% growth inhibition	MTT assay (48 h)	Akao et al. (2008)
Oral cancer	Ca9-22, HSC-3, TSC-15	50 μM	35 ~ 80% growth inhibition	MTT assay (72 h)	Yang et al. (2020)
Osteosarcoma	U2OS	50 μM	20% growth inhibition	Alamar blue assay (24 h)	Lellupitiyage Don et al. (2020)
	U2OS, HOS, MC3T3-E1	0 ~ 100 μM	Non ~ toxic	MTT assay (24 h)	Cheng et al. (2016)
Ovarian cancer	OVCAR-3, A2780/CP70	160 μM	70% growth inhibition	MTS assay (24 h)	Chen et al. (2015)
	SKOV3, HO-8910, ES-2, CaoV3	40 μM	25% growth inhibition	MTT assay (24 h)	Jiang, Guo, and Wang (2018)
	A2780	0.5 ~ 9 μM	IC_{50} = 25.12 ± 4.7 μM	SRB assay (48 h)	Ma et al. (2015)
	A2780	0 ~ 50 μM	IC_{50} = 35.31 μM	CCK-8 assay (24 h)	Zhang et al. (2020c)
	OVCAR-3		IC_{50} = 34.85 μM		
	OVCAR-3	20, 40 μM	20.07%, 28.53% growth inhibition	MTS assay (24 h)	He et al. (2015)
	A2780		19.73%, 36.92% growth inhibition		
Pancreatic cancer	MIA-PaCa-2	0 ~ 100 μM	IC_{50} = 6.12 μM	CCK-8 assay (24 h)	Jiang et al. (2020)
Prostate cancer	PC-3	80 μM	50.33% growth inhibition	WST-1 assay (48 h)	Deveci Ozkan et al. (2020)
	LNCaP	20 μM	51.39% growth inhibition		
	PC-3	0 ~ 160 μM	IC_{50} = 117 μM	MTS assay (24 h)	Chen et al. (2014b)
	DU-145		IC_{50} = 137 μM		
	LNCaP	1×10^{-6} M ~ 1×10^{-3} M	IC_{50} = 1.3×10^{-4} M	WST-1 assay (48 h)	Tang et al. (2007)
	DU145		IC_{50} = 1×10^{-4} M		
	PC-3		IC_{50} = 2.7×10^{-4} M		
	PC-3	80 μM	46.99% growth inhibition	WST-1 assay (48 h)	Guney Eskiler et al. (2019)
Squamous cell carcinoma	HBT43	8 μg/ml	70% growth inhibition	Hemocytometer (3d)	Kandaswami et al. (1991)
	TCA-8113	150 μM	25% growth inhibition	CCK-8 assay (72 h)	Lin et al. (2020)
	CAL-27		20% growth inhibition		
Thyroid cancer	PCCL3	0 ~ 100 μM	IC_{50} = 121.6 μM	MTS assay (72 h)	Sousa et al. (2020)
	T235		IC_{50} = 118.9 μM		
	T238		IC_{50} = 145.1 μM		

pathway and the intrinsic (death receptor) pathway (Elmore 2007). The activation factors of the endogenous pathway include a series of pressures such as DNA damage, endoplasmic reticulum pressure, reactive oxygen species up-regulation and oncogene expression. When the signal transmits to the mitochondria to decrease the membrane potential, Bax/Bcl-2 protein recruits in the mitochondrial outer membrane and changes the conformation of the mitochondria. The formation of mitochondrial permeability transition pore (mPTP) on the mitochondrial outer membrane promotes the release of pro-apoptotic factors such as cytochrome C into the matrix. This activates apoptotic body protein complexes (including cytochrome C, APAF1 and caspase-9 protein precursors) and apoptosis initiation enzyme (caspase-9), which further initiates downstream effector enzymes (caspase-3 or −7) leading to apoptotic cell death (Wang et al. 2018a). The exogenous apoptosis pathway is activated by combining tumor necrosis factor family death ligands (TNF-α, FasL, TRAIL, etc.) to their corresponding cell membrane surface receptors (TNFR, Fas, TRAILR, etc.). Once it binds, the multi-protein complex would form and provide a platform for activating the apoptotic initiating enzyme Caspase-8, while the activation of Caspase-8 would further activate downstream apoptotic effector enzymes such as caspase-3 or −7, and promote apoptosis (Mohana-Kumaran et al. 2014). Apoptosis is considered the best way to kill tumor cells because it does not cause inflammatory damage to surrounding tissues, and many natural products have been reported to play anti-tumor effects aimed at inducing apoptosis of cancer cells (Wang et al. 2018b).

NOB can induce apoptosis in many kinds of cancer cell lines, including bladder cancer (Goan et al. 2019), breast

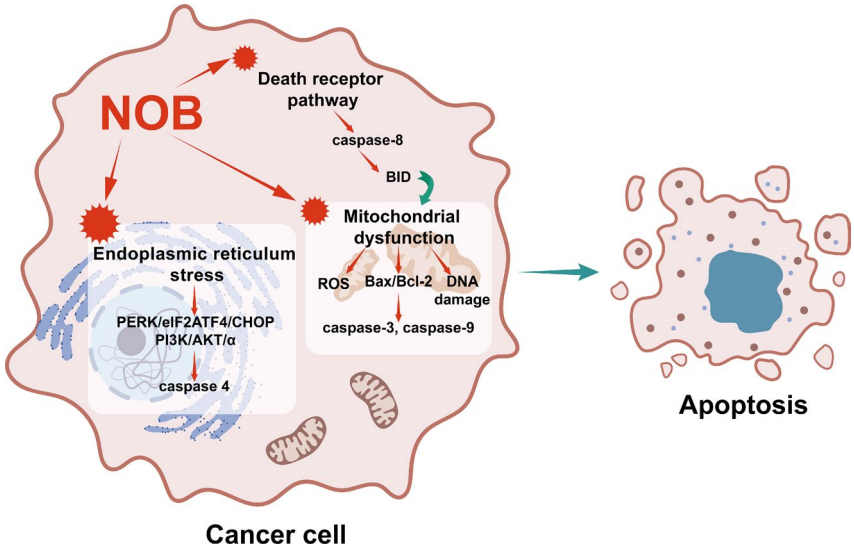

Figure 2. Nobiletin induces apoptosis of cancer cells through intrinsic and extrinsic pathways.

cancer (Liu et al. 2018b), cervical cancer (Kim et al. 2010), choriocarcinoma (Zhang et al. 2020b), colon cancer (Wu et al. 2015), gastric cancer (Moon and Cho 2016), kidney cancer (Wei et al. 2019), leukemia (Hsiao et al. 2014), liver cancer (Yousef et al. 2020), lung cancer (Moon et al. 2018), nasopharyngeal carcinoma (Zheng et al. 2019), neuroblastoma (Akao et al. 2008), oral cancer (Yang et al. 2020), ovarian cancer (Jiang, Guo, and Wang 2018) and prostate cancer (Guney Eskiler et al. 2019). This shows that promoting apoptosis is an important and common way for NOB to inhibit the growth of cancer cells. Simultaneously, in different tumor types, NOB plays its role in promoting apoptosis through different signal pathways, including mitochondrial pathway, endoplasmic reticulum pathway and death receptor pathway (Figure 2), often in a concentration-and time-dependent manner.

Mitochondrial dysfunction plays a critical role in the endogenous pathway of apoptosis induced by NOB. Mitochondrial dysfunction could induce the expression of pro-apoptotic proteins including Bak, Bad, Bid, Bim and PUMA, and reduce the expression of anti-apoptotic proteins like Bxl-2, Bcl-xl, p-Bad and Mcl-1. The disruption of the balance between Bax and Bcl-2 would increase mitochondrial membrane permeability and release cytochrome C to the cytoplasm. This could activate the caspase family proteins, in which caspase-3 and caspase-9 are considered to play a leading role (Goan et al. 2019). Apoptosis of gastric cancer SUN-16 cells induced by NOB was achieved by increasing the ratio of Bax/Bcl-2 protein, activating caspase-9, caspase-3, caspase-7 and cleavage of PARP (poly ADP-ribose polymerase) (Moon et al. 2013). Similar mechanisms have been found in kidney cancer (Wei et al. 2019) and liver cancer cells (Ma et al. 2014). When oral squamous cell carcinoma (OSCC) cells were treated with NOB, the levels of caspase-3 and PARP gradually increased with the increase of NOB concentration and treatment time, as did oxidative stress and DNA damage (Yang et al. 2020). Studies have shown that colonic metabolites of NOB could also strongly induce caspase cascade activation, cleavage caspase-3 and caspase-9 and their final protein target PARP in human colorectal cancer cell line HCT116, and the effect is much stronger than that of NOB alone (Wu et al. 2015).

In addition to the mitochondrial pathway, endoplasmic reticulum stress can also mediate NOB-induced apoptosis. After NOB treatment of bladder cancer cells (BFTC), endoplasmic reticulum (ER) stress was initiated by PERK/eIF-2ATF4/CHOP pathway and down-regulated PI3K/AKT/α pathway, followed by apoptosis induction (Goan et al. 2019). In gastric cancer cells SNU-16, NOB increased the levels of endoplasmic reticulum stress-related proteins inositol requiring enzyme 1α (IRE1-α), activating transcription factor 4 (ATF4), C/EBP homologous protein (CHOP) and GRP78, and activated endoplasmic reticulum stress-mediated apoptotic protein caspase-4 (Moon and Cho 2016).

Moreover, endogenous and exogenous apoptotic pathways could be linked through BID proteins in the Bcl-2 family that contain only the BH3 domain. Activated caspase-8 could cleave BID to form tBID, while tBID would directly activate pro-apoptotic proteins (Bax and Bak) in the endogenous pathway or indirectly inhibit anti-apoptotic proteins in the endogenous pathway, resulting in endogenous apoptosis (Galluzzi et al. 2016). Treatment with NOB-rich chloroform of *Angelicasinensis* (CF) could simultaneously induce the activation of caspase-8 and caspase-9 in HeLa cells of cervical cancer, which upregulated the cleavage of procaspase-8 and sharply increased the cleavage of BID, leading to the activation of caspase-9 and −3 (Goan et al. 2019). This indicates that NOB-mediated apoptosis may be closely related to the tandem of endogenous pathways and exogenous pathways. At the same time, p38 MAPK(Liu et al. 2018b), Parp-2/SIRT1/AMPK(Zheng et al. 2019), STAT3/JAK2/C-Src (Chiang et al. 2012), PI3K/AKT/mTOR (Jiang, Guo, and Wang 2018), COX-2 (Ma et al. 2014) and other signaling pathways may also be involved in the mechanism of NOB in promoting cancer cell apoptosis.

However, after 100 μM NOB treatment of human choriocarcinoma trophoblast cells (BeWo cells) for 48 h, the expressions of Bcl-2 and Bcl-xl increased and the accumulation of p53 decreased, but the level of Bax, BAK, BAD, p21 and G1 phase arrest showed no significant changes. This proved that NOB may inhibit the apoptosis of BeWo cells at this concentration and was safe for BeWo cells (Zhang et al. 2020b).20–30 μM NOB had a preventive effect on H_2O_2-induced apoptosis of human neuroblastoma SH-SY5Y cells and weakened the activation of endogenous apoptotic pathways (Akao et al. 2008). NOB could not effectively induce apoptosis of MOLT-4 and MOLT-4/DNR cells at a concentration (100 μM) that almost completely inhibited cell growth, reflecting that the biological effect of NOB was most related to cell inhibition rather than cytotoxicity (Ishii et al. 2010). In conclusion, both the concentration of NOB and the type of tumor cell lines can affect the regulatory effect of NOB on cancer cell apoptosis.

Cell cycle arrest

The cell cycle is a complex and orderly set of events that ultimately lead to cell growth and division. The cell cycle consists of G1 (pre-replication phase), S (DNA replication phase), G2 (post-DNA synthesis), and M (mitosis). Among them, the restriction points in the G1/S phase and G2/M phase are two key points to ensure the quality of DNA replication (Candas et al. 2013). The cell cycle regulatory proteins can be divided into three categories, including cyclin, cyclin-dependent kinase (CDK) and CDK inhibitory protein (CKI). Different cyclins can combine with different CDKs to form a cyclin-CDK complex to regulate different cell cycle stages. CKIs (including P21 and P27, etc.) can exert a specific inhibitory effect by binding to CDKs. The cell cycle regulation is mainly achieved by regulating cyclin kinase expression (Tsai et al. 2017). During tumor growth, abnormal cell cycle regulations may lead to dysregulation of cell cycle redistribution, accelerate DNA damage repair and cycle process, and ultimately cause tumor progression (Rubicz et al. 2015). Therefore, taking the cell cycle as the target, selecting new drugs that protect normal tissue and induce the differentiation or apoptosis of tumor cells to regulate the tumor cells deviating from the normal cell cycle track to return to the regular track is a new strategy of anti-cancer therapy at present.

Similar to inducing apoptosis, NOB can affect the cell cycle progression of various cancer cells, including breast cancer (Surichan et al. 2018), colon cancer (Silva et al. 2018), gastric cancer (Yoshimizu et al. 2004), glioma (Lien et al. 2016), kidney cancer (Wei et al. 2019), leukemia (Saito, Abe, and Nogata 2020), liver cancer (Ma et al. 2014), lung cancer (Uesato et al. 2014), oral cancer (Lin et al. 2020), pancreatic cancer (Jiang et al. 2020), prostate cancer (Chiang et al. 2012) and thyroid cancer (Sousa et al. 2020). This is achieved via different possible routes. In general, NOB can regulate the expression of different proteins, mainly down-regulating positive regulators of the cell cycle to induce the cell cycle arrest of cancer cells (Figure 3). It induces cell cycle arrest in the G1 phase in most cell lines, such as breast cancer, colon cancer, gastric cancer, etc. In three breast cancer cell lines (MCF-7, SK-BR-3, MDA-MB-468), NOB significantly delayed the G0/G1 phase of the cell cycle, inhibited the activity of ERK1/2 and the up-regulation of cyclin D1 and p21 (Chen et al. 2014a). Similarly, NOB caused the inactivation of RB signal by down-regulating the expression of cyclin D1, CDK2, CDK4 and E2F1, while prevented the growth of glioma cells U87 by blocking the cell cycle at the G0/G1 phase (Lien et al. 2016). Surichan et al. found that NOB induced its metabolism by upregulating the activity of cytochrome P450 CYP1 family enzymes, thereby enhancing its cell inhibition on breast cancer cells (Surichan et al. 2012; Surichan et al. 2018). In the research of colon cancer and breast cancer cells, NOB (60 ~ 100 μM) was found to induce G1/S phase arrest of cells and significantly inhibit cell proliferation without any apoptosis/death, which contributed to protecting normal tissues from toxic side effects (Morley, Ferguson, and Koropatnick 2007). NOB could also change the cell cycle distribution of human acute myeloid leukemia cells and promote cell differentiation. After THP-1 cells were treated with NOB (20,40 and 80 μM) for 48 h, the cell population in the G1 phase was significantly increased, and the expression of monocyte differentiation marker gene CD11bmRNA increased to 1.9-, 2.9- and 4.8-fold higher than that in the blank control group, respectively (Moon et al. 2013). In addition, NOB and its different colon metabolites have different effects on the cell cycle progression of human colon cancer cells. For example, NOB, 3′-demethylnobiletin and 3′,4′-didemethylnobiletin would block human colon cancer HCT116 cells in G0/G1, S and G2/M phases, respectively, while 4′-demethylnobiletin blocked HCT116 cells in G0/G1 and G2/M phases simultaneously(Wu et al. 2015). When NOB and its colonic metabolites act in combination, they could arrest the cell cycle at G0/G1 or G2/M stages and inhibit cell growth, significantly reduce the levels of cyclin D, CDK6, CDK4 and CDK2 proteins, and increase the levels of p27 and p53 proteins (Wu et al. 2017a).

NOB also can block the cell cycle of tumor cells such as liver cancer and lung cancer at G2/M phase. In MH1C1 cells, NOB treatment significantly increased the number of cells in G2 or M phase and decreased the cell proportion in S phase, while in HepG2 cells, NOB also brought a dramatic increase of cell numbers in G2 or M phase. This is closely related to the down-regulation of cell cycle-related genes cyclin E, cyclin B and Bcl-2 (Ohnishi et al. 2004). Similar phenomena were observed in SMMC-7721 cells (Ma et al. 2014). Additionally, NOB could activate p53 through DNA damage and inhibit the growth of lung cancer cells A549, resulting in cell cycle arrest in the G2/M phase (Luo, Guan, and Zhou 2008). There are few studies on the biological effects of NOB on thyroid cancer, but the latest studies have found that NOB reduced the activity of ATC (T235 and T238) in a dose-dependent manner without affecting the cell cycle distribution (Sousa et al. 2020). These findings suggest that NOB has different regulatory effects in different cancer cells, possibly due to different biotransformation of different tissues, and its metabolites

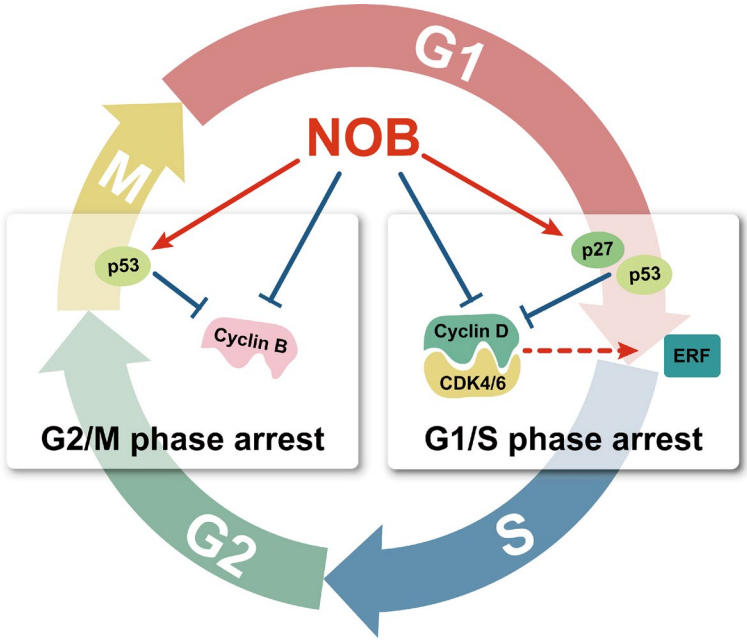

Figure 3. Nobiletin can induce G1/S phase arrest and G2/M phase arrest in cancer cells.

may exhibit diverse biological effects depending on the tissues they interact with.

Autophagy regulation

Autophagy is an evolutionarily highly conserved, lysosomal-mediated self-feeding mechanism. It involves forming bilayer membrane vesicles (autophagosomes) that engulf cytoplasmic contents and transport the contents to lysosome degradation. Autophagy is a natural catabolism process. The degradation and recycling of cytoplasmic substances in lysosomes are highly important for controlling cell death (Zhuang et al. 2018).

Current studies have found that autophagy plays a dual role in the development of cancers. On the one hand, autophagy can reduce the incidence of precancerous cell transformation and exert its anti-tumor effect in many ways, such as maintaining the stability of the genome, clearing the excessive production of reactive oxygen species in the cell, degrading and scavenging carcinogenic proteins such as p62, activating the function of the anti-tumor immune system, and so on (Galluzzi et al. 2016; Inami et al. 2011). On the other hand, its ability to relieve the environmental pressure in tumor cells (such as hypoxia, hunger) can promote tumor development in the later stage(Guo, Xia, and White 2013). In recent years, the application of genetically engineered murine models (GEMMs) in cancer research has further proved that the deletion of autophagy-related genes contributes to early tumors and harms the development of tumors in the middle and later stages (Rao et al. 2014).

Recent studies have demonstrated that NOB can induce the autophagy of cancer cells (Figure 4). It is known that PI3K/AKT and its downstream mTOR are critical regulators in initiating autophagy, and the inhibition of this pathway is related to autophagy induction (Meijer and Codogno 2009). At the same time, the formation of autophagosomes involves the expression of p62 and the conversion of LC3 from cytosolic LC3-I to autophagosome-related LC3-II (Zhuang et al. 2018). SNU-16 apoptosis induced by NOB was achieved by protective autophagy mediated by endoplasmic reticulum stress. After NOB treatment, the phosphorylation levels of AKT and mTOR decreased significantly, while the ratio of LC3B-II/LC3B-I increased, and the level of p62 decreased (Moon and Cho 2016). This kind of autophagy induced by endoplasmic reticulum stress can effectively remove toxic proteins in the endoplasmic reticulum and protect cells, so the correlation of NOB and autophagy inhibitors may improve treatment outcomes of gastric cancer. NOB could also induce autophagy and inhibit the growth of MIAPaCa-2 human pancreatic cancer cells, accompanied by increased expression of LC3- II and LC3-Iand decreased expression of p62 (Jiang et al. 2020). What's more, in ovarian cancer cell line A2780 and OVCAR3, NOB resulted in both classical autophagy and mitochondrial autophagy, which further induced cell pyroptosis and reduced the growth of the ovarian cancer cell lines (Zhang et al. 2020c). It can be seen that there is a complex relationship between autophagy and apoptosis and the effect on cancer, which depends on different cell lines.

Invasion and migration inhibition

Cancer cell invasion refers to the local invasion or distant metastasis of cancer cells. Cell migration, also known as cell crawling, cell locomotion or cell movement, refers to the movement produced of cells after receiving the migration signal or sensing the gradient of some substances. The invasion and migration of cancer cells are often the main factors affecting the prognosis of patients. The main pathways that

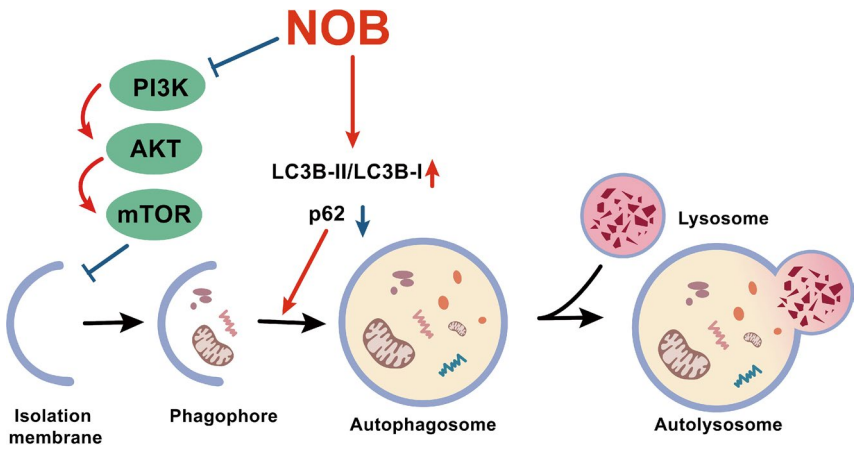

Figure 4. Nobiletin regulates autophagy through PI3K/AKT/mTOR pathway.

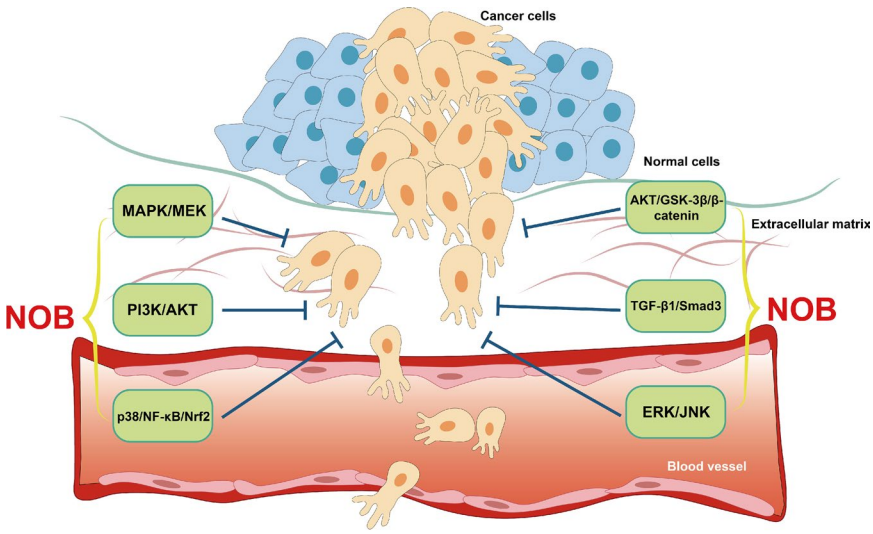

Figure 5. Nobiletin inhibits invasion and migration of cancer cells through multiple pathways.

inhibit invasion and migration are MAPK/MEK signal pathway, PI3K/AKT pathway, p38/NF-κB/Nrf2 pathway, TGF-β1/Smad3 signal pathway, ERK/JNK signal pathway and AKT/GSK-3β/β-catenin signal pathway (Figure 5).

Matrix metalloproteinases (MMPs), a zinc-dependent family of endopeptidases, play an essential role in these pathways. Several members of the MMP family are associated with cancer invasion(Klein et al. 2004). In particular, MMP-9 could degrade basement membrane components related to cancer metastasis and invasion. The mitogen-activated protein kinases (MAPK) family comprises serine/threonine kinases that mediate intracellular signal transduction. C-Jun NH_2-terminal kinase (JNK) is a member of MAPK family. It is an evolutionarily conserved serine and threonine protein kinase that can bind the NH_2-terminal of c-Jun and activate c-Jun. CXC chemokine receptor-4 (CXCR4), the most characteristic chemokine receptor, could induce leukocyte migration(Hernandez et al. 2003). MAPK signaling pathway is an important signal transduction system for eukaryotic cells to mediate extracellular signals to intracellular reactions. It conducts extracellular signals in the form of a three-stage kinase cascade. That is, the extracellular signals → MAPK kinase kinase (MKKK) → MAPK kinase (MKK) → MAPK, regulating a variety of physiological processes such as cell growth, differentiation, apoptosis, and death. This pathway relies on the participation of extracellular signal-regulating protein kinase (ERK1/2), c-Jun NH_2-terminal kinase/stress-activated protein kinase (JNK/SAPK), p38 lightning MAPK and ERK5.

It was reported that NOB showed anti-cancer invasion activity in vitro and in vivo by inhibiting the production of pro-matrix metalloproteinases (ProMMPs) and upregulating the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) (Miyata, Sato, and Ito 2005). NOB could also enhance the phosphorylation of JNK, a signal factor downstream of PI3K/AKT pathway. TIMPs −1, 2, 3, and 4, could inhibit the enzyme activity of MMPs (Brew, Dinakarpandian, and Nagase 2000), which in turn suppressed the invasion and metastasis of malignant tumor cells (Sato et al. 1999), such as reducing the adhesion, invasion and migration of the high metastatic AGS gastric adenocarcinoma cells (Lee et al. 2011) and decreasing the proliferation and migration

of U87 glioma cells(Lien et al. 2016). Baek et al. (2012) showed that NOB down-regulated the expression of chemokine receptors CXCR4 and MMP9 in human breast cancer cells by inhibiting the activation of NF-κB and MAPK signal pathway, thus effectively inhibiting the invasion and migration of tumor cells (Baek et al. 2012). Fan, Mao, and Yang (2013) also demonstrated that NOB could inhibit peritoneal metastasis of human gastric cancer cells in SCID mice by inhibiting the enzyme activity of MMP-9 (Fan, Mao, and Yang 2013). And Rooprai et al. (2001) also found down-regulated expression of MMP-2 and MMP-9 gelatinases in grade 3 astrocytomas, which confirmed the role of NOB in reducing the invasion, migration and adhesion of brain tumor cells (Rooprai et al. 2001).

The activation of MAPK/MEK signaling pathway is closely related to cancer invasion and metastasis. It showed that NOB would decrease the activity of extracellular signal-regulated kinase (MEK) and inhibit the phosphorylation of extracellular regulated kinase (ERK), thus down-regulating the expression of MMP in human fibrosarcoma HT-1080 cells stimulated by tumor metastasis stimulating factor 12-myristate phorbol 13-acetate (TPA) (Miyata et al. 2008).

The PI3K/AKT pathway mainly affects the distant metastasis of cancer cells by reducing the adhesion between tumor cells. Adhesion molecules, such as E-cadherin, are membrane surface glycoproteins with adhesion, forming adhesion between cells and between cells and stroma, preventing tumor cells from detuning from cancer tissues and inhibiting cancer cell infiltration. Studies by Shukla et al. (2007) and Chen et al. (2014b) showed that the expression level of p-AKT is a manifestation of the activation of the PI3K signaling pathway, and the upregulation of p-AKT expression can promote the invasion and metastasis of prostate cancer cells. (Chen et al. 2015, Shukla et al. 2007). In addition, NOB has been proved to down-regulate the expression of MMP-1 and MMP-9 in transcription through PI3K pathway, and upregulate the expression of TIMP-1 to inhibit the in vitro invasion of HT-1080 cells (Sato et al. 1999). In liver cancer, NOB could also significantly reduce the levels of phosphorylated ERK2 and phosphorylated AKT in ERK2 or AKT siRNA transfected cells, thus inhibiting the metastasis of HepG2 cells involving ERK and PI3K/AKT pathways induced by hepatocyte growth factor (HGF) (Shi et al. 2013).

The p38/NF-κB/Nrf2 pathway would up-regulate the level of p38 phosphorylation and reduce the translocation of p65 and Nrf2, then inhibiting the migration of cancer cells. Liu et al. (2018a) showed the decreased expression of Bcl-2 in McF-7 cells treated with NOB, while the expression of Bax and p53 increased. Meanwhile, NOB inhibited cell migration by down-regulating MMP-2 and MMP-9 (Liu et al. 2018b).

In TGF-β1/Smad3 signaling pathway, epithelial-mesenchymal transformation (EMT) is an essential cellular process during cancer metastasis, in which epithelial polarized cells are transformed into movable mesenchymal cells. Smad3 is necessary for EMT stimulated by transforming growth factor-β1 (TGF-β1). Overexpression of Smad3 can significantly reduce the ability of NOB to reverse endometrial stromal transformation induced by TGF-β1. It showed that NOB could successfully inhibit the endothelial cell metastasis, migration, invasion and adhesion induced by TGF-β1, and inhibit the expression of MMP-2, MMP-9, p-SRC, p-FAK, p-paxillin, Snail, Slug, Twist and ZEB1, thereby inhibiting the epithelial-mesenchymal transformation of human non-small cell lung cancer cells (Da et al. 2016).

ERK/JNK pathway could inhibit the activities of extracellular signal-regulated kinase and c-Jun N-terminal kinase, decrease the mRNA expression and protein level of MMP-2 and MMP-9, and inhibit the DNA binding activity of transcription factors nuclear factor-kappa B (NF-κB), cAMP response element-binding protein (CREB) and specific protein-1 (SP-1) in tumor cells. Cheng et al. (2016) pointed out that NOB inhibited the movement, migration and invasion of human osteosarcoma U2OS and HOS cells by down-regulating the expression of MMP-2 and MMP-9, and by inactivating downstream NF-κB, CREB and SP-1 (Cheng et al. 2016). Additionally, in human nasopharyngeal carcinoma cell lines, NOB also participated in the transcriptional inhibition of ERK1/2 and MMP-2 (Chien et al. 2015)

In AKT/GSK-3β/β-catenin signal pathway, glycogen synthase kinase-3β (GSK-3β) is a serine/threonine kinase that recognizes and phosphorylates specific sequences. The function of β-catenin is primarily to mediate cell adhesion and participate in gene expression. NOB has been indicated to inhibit the invasion of glioma cells by inhibiting AKT/GSK-3β/β-catenin signal pathway. During this process, the expression of epithelial markers (E-cadherin and occludin) was up-regulated, while the expression of mesenchymal markers (N-cadherin and FN) and transcription factor (slug) was down-regulated.

Angiogenesis inhibition

Angiogenesis is an essential condition to maintain the continuous growth of tumors. As compensation for insufficient blood supply, nutrients and oxygen can be delivered to the tumor nodules to convert tumors from a dormant state to a malignant state (Ferrara 2004, McDougall, Anderson, and Chaplain 2006). Therefore, to limit the growth of solid tumors, angiogenesis inhibition or vascular prevention, is considered to be a promising strategy for the development of anticancer therapies (He et al. 2015). Vascular endothelial growth factor (VEGF) is an expected growth factor that induces vascular growth in a variety of cancers (Weng and Yen 2012). VEGF expression promotes angiogenesis, which is an essential factor in cancer growth and metastasis and plays a core role in the development and maintenance of cancer blood vessels. As a critical regulator of angiogenesis in ovarian cancer, VEGF participates in all aspects of ovarian carcinogenesis. Thus, identifying compounds that inhibit VEGF secretion would be helpful in preventing cancer growth.

There are three major pathways that suppress angiogenesis, including PI3K/AKT, Src/FAK/STAT3, and CD36/STAT3/NF-κB signal transduction pathway (Figure 6).

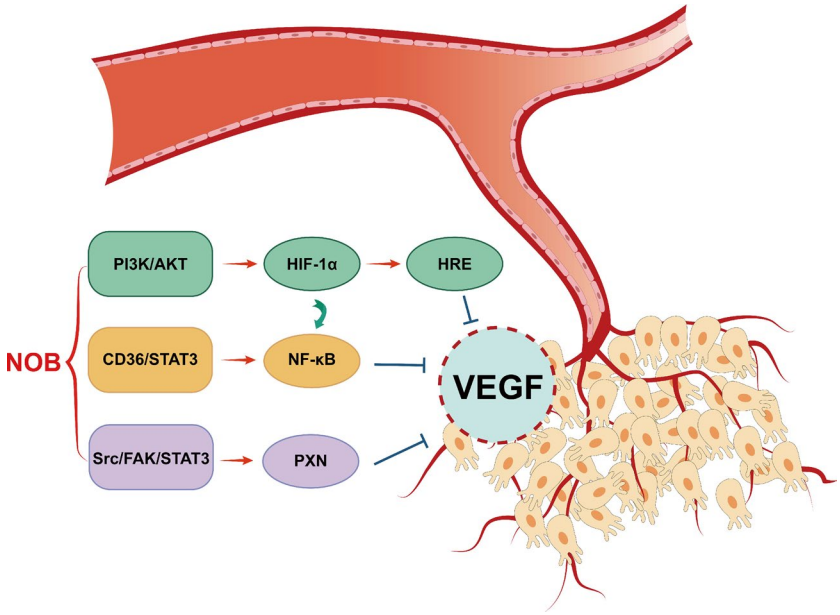

Figure 6. Nobiletin targets VEGF to inhibit cancer angiogenesis in three major pathways.

Activation of the PI3K/AKT pathway is a vascular endothelial signaling pathway through forming a complex with epithelial cadherin (E-cadherin), β-catenin, and vascular endothelial growth factor receptor 2 (VEGFR-2), as well as the interaction between this complex and VEGF. Previous studies have shown that NOB inhibited the invasion and migration of human gastric adenocarcinoma AGS cells through the FAK/PI3K/AKT pathway (Lee et al. 2011). Angiogenic mediators (AKT) are considered the primary signal for cell survival and proliferation (Miura et al. 2008). The AKT signal transduction pathway controls cancer growth and angiogenesis by inhibiting AKT phosphorylation, down-regulating AKT expression, and suppressing levels of hypoxia-inducible factor-1α (HIF-1α), NF-κB, and VEGF. HIF-1α is one of the key factors regulating the activity of the angiotensin-converting enzyme, a heterodimer basic helical loop-helical protein that directly activates VEGF transcription by binding to hypoxic response element (HRE) (Forsythe et al. 1996). Hypoxia and other factors such as growth factors and insulin can act on membrane surface receptors to induce the expression of hypoxia-inducing factor-1α (HIF-1α) and promote the translation of angiogenesis genes such as downstream VEGF. Cyclooxygenase-2 (COX-2) can affect endothelial cell movement and neovascularization, and activation of PI3K/AKT signaling pathway can upregulate COX-2, thus participating in cancer angiogenesis. It has been proved that NOB could inhibit the phosphorylation of AKT and reduce the production of HIF-1α by down-regulating AKT, which is one of the reasons responsible for NOB-induced suppression of VEGF (Chen et al. 2015; He et al. 2015). NF-κB is a common transcription factor that participates in various signal transduction pathways of cancer cell proliferation and angiogenesis(Jeong and Kong 2004). Some researchers have found that the AKT pathway regulated the expression, activation and translocation of NF-κB (Kar et al. 2012; Kim et al. 2008). In addition, the importance of NF- κB in the proliferation of ovarian cancer cell lines has been confirmed (Lin et al. 2007), which acts on angiogenesis by antagonizing the expression of VEGF(Gonzalez-Perez et al. 2010). The inhibition efficacy of NOB on neoangiogenesis is likely to be an NF-κB dependent process, which has been proved to have a protective effect on endometriosis (Wei and Shao 2018).

The Src/FAK/STAT3 pathway regulated through PXN is a molecular pathway that inhibits STAT3/DNA binding activity and STAT3 binding to a novel binding site of the PXN gene promoter, down-regulates Src, FAK, and STAT3 signal transduction, thus inhibiting tumor angiogenesis. Steroid receptor coactivator (Src) and focal adhesion kinase (FAK) are intracellular tyrosine kinases, which are two key signal molecules that play an essential role in tumor angiogenesis (Sieg et al. 2000). Src induces angiogenesis by promoting the expression of VEGF (Park et al. 2007), while FAK regulates cancer angiogenesis as well as cell survival by forming a complex with Src through phosphorylation of paxillin (PXN) (Lechertier and Hodivala-Dilke 2012, Yang et al. 2017). Signal transducer and activator of transcription 3 (STAT3) is a marker of tumor angiogenesis that interacts with Src. PXN as the downstream target of FAK and STAT3 (Webb et al. 2004), plays the same role as STAT3. Moreover, Src can regulate the expression of FAK and STAT3 and then regulate the expression of PXN. Sp et al. (2017) found that NOB regulated estrogen receptor-positive (ER+) breast cancer cells through PXN and down-regulated Src, FAK and STAT3 signal transduction, thereby inhibiting tumor angiogenesis (Sp et al. 2017).

Moreover, in CD36/STAT3/NF-κB pathway, the cluster of differentiation 36 (CD36) is a member of the class B scavenger receptor family, which initiates anti-angiogenic signals by binding to its ligand thrombospondin-1 (TSP-1)

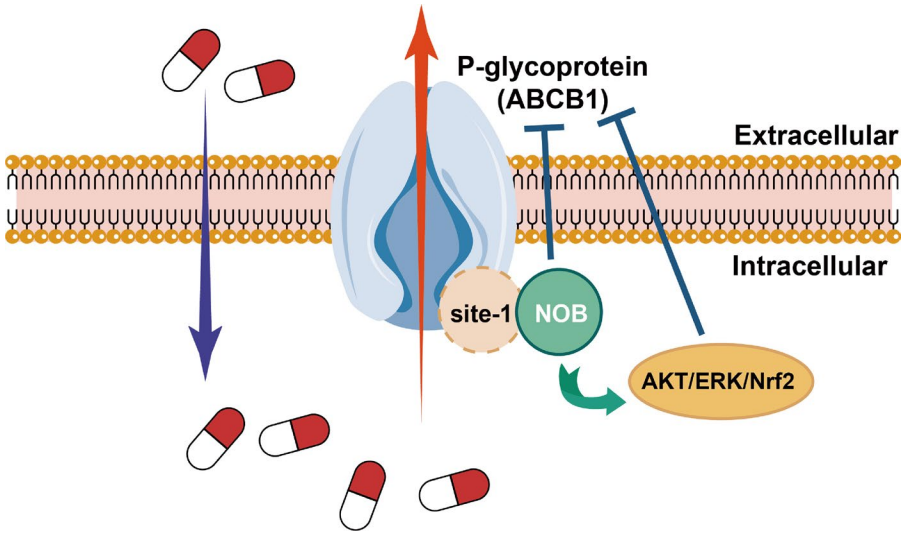

Figure 7. Nobiletin reverses multidrug resistance by targeting P-glycoprotein.

and then interacting with transforming growth factor-beta 1 (TGF-β1) (Mirochnik, Kwiatek, and Volpert 2008; Osz, Ross, and Petrik 2014; Silverstein et al. 1992). Engagement of CD36 by TSP-1 leads to inhibition of migration and tube formation through proapoptotic pathways and SHP-1–mediated pathway (Chu, Ramakrishnan, and Silverstein 2013). However, recent research suggested that CD36 also interacted with the STAT3 oncogene (Rozovski et al. 2017), and STAT3 then interacted with NF-κB in the nucleus, leading to carcinogenesis (Fan, Mao, and Yang 2013). In the targeted therapy of natural products, it was found that the anti-angiogenic activity of NOB involved its regulation of CD36 via STAT3 rather than through TSP-1 (Sp et al. 2018). Thus, NOB could inhibit cancer angiogenesis via the CD36/STAT3/NF-κB signaling axis.

Multidrug resistance relief

Multidrug resistance (MDR) of anticancer drugs is one of the critical problems in cancer chemotherapy. Reversing multidrug resistance (MDR) has become an important objective in cancer treatment, mainly including P-glycoprotein (P-gp) regulation pathway and AKT/ERK/Nrf2 signal transduction pathway (Figure 7).

The major mechanism of MDR has been attributed to P-gp function. P-gp is a 170 kDa glycoprotein overexpressed on the plasma membrane of MDR cancer cells, also known as ATP-binding cassette transporters subfamily B member 1 (ABCB1) (Gottesman, Pastan, and Ambudkar 1996). As an energy-dependent drug efflux pump, P-gp can expel anticancer drugs from cells, resulting in a decrease in intracellular drug concentration and reducing the therapeutic efficacy of a variety of chemotherapeutic drugs (Ikegawa et al. 2000). Previous researches revealed that NOB could selectively inhibit P-gp and reduce the transport of saquinavir mediated by multidrug resistance-associated protein 2 (MRP2) (Honda et al. 2004; Ohtani et al. 2007; Takanaga et al. 2000).

In addition, Ma et al. (2015) demonstrated for the first time that NOB significantly reversed ABCB1-mediated MDR by modulating the ABCB1 function and inhibiting the AKT/ERK/Nrf2 pathway (Ma et al. 2015). NOB inhibited the activity of ABCB1 transporter by competitively binding to the substrate-binding region (site-1) of the transporter, resulting in an increase in the concentration of intracellular NOB and ABCB1 substrates. It is worth noting that the combination of NOB-PTX decreased the phosphorylation level of AKT/ERK and Nrf2 expression, suggesting that the inhibition of AKT/ERK/Nrf2 pathway was strongly associated with the sensitization of NOB. Their latest research also showed that NOB and its derivatives all had the ability to inhibit MDR-efflux protein through competing with chemotherapeutic drugs for the same P-gp binding site, then improving the effectiveness of cancer chemotherapy in vitro (Feng et al. 2020). NOB could reverse MDR in paclitaxel (PTX)-resistant cells (A2780/T) by sensitizing them over 400 folds in comparison with its parent A2780 cells.

Others

Inflammation has a critical role in cancer development. Targeting cancer inflammatory microenvironment, regulating the balance of anti-cancer, and promoting cancer inflammatory response are new important directions in cancer therapy research. In prostate cancer (PCa) cells, NOB showed anti-inflammation activity by suppressing TLR4/TRIF/IRF3 and TLR9/IRF7 signaling pathways through the downregulation of their associated pathways (mRNA and related protein levels) and the release of IFN-α and IFN-β (Deveci Ozkan et al. 2020). NOB significantly inhibited two distinct stages of skin inflammation induced by double 12-*O*-tetradecanoylphorbol-13-acetate (TPA) application [first stage priming (leukocyte infiltration) and second stage activation (oxidative insult by leukocytes)] by decreasing the inflammatory parameters. It also suppressed

the expression of cyclooxygenase-2 and inducible NO synthase proteins and prostaglandin E_2 release. And in vivo experiments have shown that NOB inhibited dim-ethylbenz[a] anthracene (0.19 mmol)/TPA (1.6 nmol)-induced skin cancer formation at doses of 160 and 320 nmol (Murakami et al. 2000). For chronic gastritis and gastric cancer, NOB has shown significant activity in inhibiting the expression of CD74 (an adhesion molecule to urease in *H. pylori.*), although the mechanism of action is still unclear (Sekiguchi, Washida, and Murakami 2008).

In other researches on breast cancer, NOB had an anti-cell proliferative effect on DMBA-induced mammary cancer via modulation of the AP-1 signaling pathway (Zhang et al. 2020a). Additionally, NOB exhibited biphasic effects on aromatase activity and expression, decreasing aromatase expression at low concentration and increasing aromatase expression at high concentration (Rahideh et al. 2017b). However, the combination of hesperetin, NOB, and letrozole had no obvious effects on the activity and expression of aromatase in MCF-7 breast cancer cells (Rahideh et al. 2017a).

Natural killer (NK) cells are the first line of defense against cancer cells and virus-infected cells. Studies suggested that NOB could potentiate the cytolytic activity of KHYG-1 cells. The primary role of NOB in the activation of KHYG-1 cells is marked induction of the granzyme B gene, at least in part, mediated through p38 MAPK function (Saito, Abe, and Nogata 2015).

Furthermore, NOB would be able to elevate the efficacy of chemotherapeutic agents when combined with different chemotherapeutic drugs. In a 3 D cell model of colorectal cancer, all PMFs, including NOB, were shown to target cancer stemness and improve the antiproliferative effect of 5-fluorouracil (Pereira et al. 2019). NOB when combined with imatinib could synergistically reduce the viability of K562 cells (Yen et al. 2020). In addition, NOB could partially inhibit P-gp-mediated dasatinib efflux and greatly inhibit BCRP-mediated dasatinib efflux at the concentration of 50 μM (Fleisher et al. 2015).

Apart from that, NOB has been observed to suppress cell proliferation by inhibiting Ras activity and MEK/ERK signaling cascade, probably via a Ca^{2+}-sensitive PKC-dependent mechanism (Aoki et al. 2013). In vivo cancer models also found that higher levels of leptin in serum promote colon carcinogenesis in obese mice, whereas NOB had chemopreventive activity against colon carcinogenesis, partly through regulation of serum growth factors, such as lowering serum leptin, insulin and IGF-1 levels (Miyamoto et al. 2010; Miyamoto et al. 2008).

Outlook

Nobiletin is so effective, why hasn't it been developed into clinical medicines?

Despite having promising pharmacological activities, some restrictions have reduced NOB potential, and the preclinical and clinical utility of NOB is limited due to its poor aqueous solubility, poor permeability, low bioavailability, as well as increased first-pass metabolism (Kesharwani et al. 2020). There are no related drugs have been developed even though a large number of studies have shown the effect of NOB on cancer. To determine whether a natural product will be further developed into a new drug depends on whether the candidate drug molecules meet the corresponding drug-forming requirements, such as relative molecular mass, solubility, lipid-water partition coefficient, stability, and permeability, as well as the metabolic stability of plasma and liver microsomes, in addition to the properties such as significant drug effect, clear action mechanism, and safety. The poor drug-forming property of natural products is mainly due to the unacceptable pharmacokinetic characteristics such as low water solubility, low bioavailability and unstable metabolism. In the 1990s, many compounds were terminated in clinical trials due to unsatisfactory pharmacokinetic parameters(Kola and Landis 2004). In the process of natural products into medicine, pharmacokinetic evaluation models include Caco-2 cell prediction of drug absorption model, primary hepatocyte culture technology, liver microsomal drug metabolism model, in vivo mouse intestinal perfusion drug absorption model and so on, which have reference significance for the development of new drugs of natural products (Li et al. 2019; Li et al. 2018; Van Rymenant et al. 2018; Wang et al. 2013; Wang et al. 2017).

The biggest challenge of NOB is to increase its bioavailability to enhance the chemopreventive effect. As intraperitoneal injection has been associated with severe side effects such as ischemic stroke, oral administration seems to be a more promising route of administration at the moment (Gao et al. 2018). However, NOB has poor solubility in water (1–5 μg/mL) and minimal oral bioavailability (<1%), resulting in a decrease in its therapeutic and biological activities (Onoue et al. 2013). Notably, NOB undergoes many alterations to produce metabolites after ingestion, and this process is too fast, which further reduces the bioavailability of NOB. Thus, it is essential to develop a soluble and bioavailable form of NOB to overcome these biopharmaceutical challenges. In recent years, new advances have been made in improving the oral administration effects of natural products by using liposomes, nanoparticles embedding, and other methods (Kesharwani et al. 2020). Considering these appropriate new agents to improve the pharmacokinetics of NOB for subsequent drug evaluation may effectively advance its new drug development. Beyond that, although NOB is derived from natural sources and is generally considered a safe compound, its toxicity is not studied extensively in many cell types and tissues. Meanwhile, its intake in both acute and chronic settings might lead to changes in the body (Jordan, Murty, and Pilon 2004). Natural product pharmacy is a long-term and complex process, which requires a series of clinical trials and epidemiological studies, both of which take a long time to contact, collect data and analyze. To the best of our knowledge, there is no public data on the effects of long-term NOB intake. And most of the reported concentrations of NOB evaluated (>20 μM) were not achievable

in physiological conditions, as demonstrated by in vivo pharmacokinetic studies. Cost is also an issue associated with NOB because their yield is very low (mg to g per kg plant weight), which may be overcome by focusing research on how flavonoids could be produced by any other natural source such as microorganisms. Moreover, as NOB complexes with other secondary metabolites, vitamins, minerals and fibers, there is also a need to develop an efficient separation system that could improve the purity. Regarding the action mechanism, NOB has been independently studied to have prominent anti-cancer effect, but the effect is not significant when used in combination sometimes. For instance, the combination of NOB, hesperetin and letrozole had no effects on activity and expression of aromatase in MCF-7 breast cancer cells (Rahideh et al. 2017a), and the rats in the hesperidin, liensinin and limonin glucoside/Bacterial Ketone Glycoside mixed feed groups also did not show pro-apoptotic effect. Additionally, although NOB can inhibit the growth of cancer cells, it seems to have no noticeable effect in the early stage of cancer, and the mechanism research on the specific action time is not detailed (Koga et al. 2007).

Does nobiletin show efficacy after metabolism in vivo?

Sometimes, having biological activity does not mean that there is a prospect for developing new drugs. Generally, the separated and purified monomers or components are subjected to corresponding biological activity measurement to obtain various degrees of activity and disease treatment effects. However, the vast majority of natural compounds have weak biological activity and extensive effect on targets, that is, their nonspecific effects are apparent and their action targets are unclear. The most important defect is that they are not strong in drug-forming property and have no value for further development. It is necessary to structurally modify the natural compounds obtained through separation and purification to improve their biological activity and drug formability, or even to reconstruct the molecular structure fragments of the molecular functional groups through the structure-activity relationship of the compounds, to finally obtain acceptable candidate drug molecules (Montané et al. 2020; Rampogu et al. 2019). The antiproliferative effects of hesperetin (de Oliveira, Santos, and Fernandes 2020), hesperidin (Cincin et al. 2018, Ghorbani et al. 2012), NOB (Rahideh et al. 2017a), apigenin (Pham et al. 2021) have been reported in the cell culture experiments in previous studies. However, the apparent inconsistency between in vivo and in vitro studies suggests that the metabolism of natural products may alter their effectiveness in in vivo systems, thereby affecting their function. For example, it was demonstrated that apigenin-7-glucoside could be metabolized into apigenin in the aglycone form and into naringenin (and other compounds) at a low level in vivo (Hanske et al. 2009). Therefore, although apigenin effectively inhibits proliferation in vitro, its ability to affect such changes in vivo may have been reduced by its metabolism in the intestinal tract. In addition, curcumin at a concentration of 25 μM was degraded within 10 min to produce feruloyl methane and ferulic acid, with only 10% of the samples remaining (Zhu et al. 2017). In 1997, it was reported that curcumin could not be detected in serum or its concentration was shallow after oral administration of 2 g curcumin to volunteers (Wang et al. 1997). Bioavailability is poor due to rapid metabolism in the liver and intestinal wall. Similarly, this may also be the reason why it is difficult for NOB to be used as a medicine, but few studies have been conducted on the metabolism of NOB in vivo.

What future research should focus on?

This article reviews the effects and mechanisms of NOB on many different cancers and provides a theoretical idea for natural products to play a role in cancer chemoprevention. However, single target intervention is not effective in the treatment of cancer, especially in complex human systems. There are large individual differences in higher biological systems, suggesting that specific doses of individual natural products may be beneficial to some people and harmful to others. Therefore, if we are to pursue the goal of individualized medication and nutritional advice, more research in this area is needed to determine the optimal nutritional status. On this basis, the dose-effect relationship, dose range, and time-effect relationship should be paid attention to in vitro experimental design of NOB correlation, and there should be a good positive compound control. A highly recognized pharmacodynamic model is also required to evaluate the effect of the candidate compounds. It is worth noting that many dietary phytochemicals are considered to be nontoxic because of their low bioavailability, while toxicity should be a concern after systemic bioavailability is markedly increased (Yang 2020). When the safety evaluation shows that it has development potential, the initial research on the action mechanism of specific targets (such as receptors, enzymes, ion channels, structural proteins) can be considered, followed by later clinical trials. In addition, appropriate structural modification of the compounds is believed to improve the biological activity of the functional ingredients against targets, reduce nonspecific and toxic side effects, and also improve the moldability of the drug. This would have important reference significance for future research and development of NOB as drug-resistant drugs.

Disclosure statement

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