Natural Product Sciences
26(2) : 109-117 (2020)
https://doi.org/10.20307/nps.2020.26.2.109

<Review>

Natural Products Targeting Wnt/β-catenin Signaling Pathway

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Abstract – The canonical Wnt/β-catenin signaling pathways play an important role in the embryonic development, cell proliferation, differentiation, and adhesion. Therefore, the abnormal activation and repression have been associated with uncontrolled homeostasis in human tissues. In particular, the activation of Wnt signaling is highly correlated with a diverse of diseases including cancer. On this regard, a strategy for targeting Wnt/β-catenin signaling has been employed in the discovery and development of antitumor agents. Herein, the evolution of Wnt signaling and the Wnt inhibitors derived from natural products were briefly summarized in the drug discovery of anticancer agents.
Keywords – Wnt signaling, tissue homeostasis, natural products, Wnt inhibitor, cancer

Introduction

Wnt is a highly conserved signaling pathway that controls various biological and physiological activity.[1] Wnt is originated from int/Wingless family, where integration 1 (int1) is initially discovered as a mouse proto-oncogene and Wingless (Wg) gene in *Drosophila* as a functional gene for embryonic development.[2,3] Wnt signaling plays a significant role in cell proliferation, differentiation, gene transcription, and cell adhesion.[4] Although Wnt signaling has been studied for several decades in many disease models, drug discovery targeting Wnt signaling remains challenging due to its molecular complexity. Since Wnt signaling controls the tissue homeostasis, both abnormal activation or repression of Wnt signaling are associated with a variety of diseases.[5] Inactivation of Wnt signaling leads to dysregulation of hair regeneration,[6] bone formation,[7] wound healing,[8] aging in eyes,[9] and synapse generation.[10] On the other hand, activation of Wnt signaling is related to acute kidney injury,[11] lung disease,[12] and carcinogenesis.[13-16] Because targeting Wnt signaling affects many pathways, various side effects are also reported for Wnt inhibitors such as bone toxicity.[17] Therefore, it is also important to find a way to avoid the on-target toxicity by understanding the Wnt signaling pathway. In this review, we will focus on the Wnt signaling in cancer development and discuss about the role of natural products in the anticancer drug discovery by targeting Wnt signaling pathway.

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Wnt signal transduction pathways

The Wnt family consists of 19 human proteins and binding of Wnt to cell membrane receptors activate the signal transduction pathway, and Wnt signaling pathway refers signaling pathway mediated by *Wnt* gene.[18] Wnt activates diverse cellular signaling pathway via canonical or non-canonical way. The most studied role of Wnt pathway is canonical signaling which causes accumulation of β-catenin (Fig. 1), while non-canonical pathway does not involve β-catenin.[19] In normal condition, the cytoplasmic β-catenin is constantly degraded by Axin complex in the absence of Wnt.[20] The Axin complex is mainly composed of the scaffolding protein Axin, *adenomatous polyposis coli* gene product (APC), glycogen synthase kinase 3 (GSK3), and casein kinase 1 (CK1). The presence of this complex allows the E3 ubiquitin ligase subunit, β-transducin repeat-containing protein (β-TrCP), to induce β-catenin ubiquitination and proteasomal degradation.[21] The APC complex also can directly regulate the endocytosis of Wnt signaling and inhibits the constitutive activation of Wnt receptor.[22] In addition, the binding of Dickkopf (Dkk) family to lipoprotein receptor related protein 5/6 (LRP5/6) ligand inhibits the Wnt activation.[10] Frizzled (FZD) receptor is a G protein-coupled receptor (GPCR), and there are 10 FZD isoforms in mammals.[23] When Wnt protein binds to the FZD

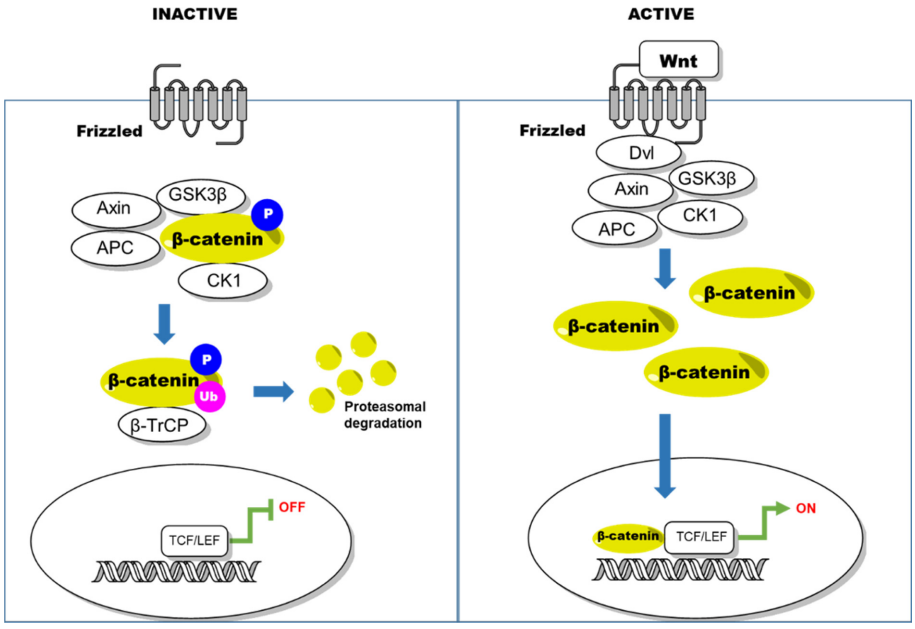


Fig. 1. The canonical Wnt signaling pathway.

receptor with LRP5/6, the scaffolding protein Dishevelled (Dvl) is recruited, and the Axin complex is dissociated which prevents the degradation of β-catenin. The Axin complex is dissociated, and β-catenin degradation is prevented.[24] This event subsequently allows β-catenin to enter the nucleus and binds to T cell factor/lymphoid enhancer factor (TCF/LEF). The accumulation of stabilized β-catenin to the nucleus activates Wnt target gene expression such as C-Myc, Survivin, and Cyclin D1.[25,26]

Additionally, β-catenin binds to the cadherins and regulates structural organization and function. Because β-catenin plays a role at the plasma membrane, the change of their interaction can also regulate Wnt/β-catenin signaling, loss of cell-cell adhesion, and E-cadherin gene transcription.[27,28] The transcription of E-cadherin can be controlled by its repressors such as Zinc finger proteins of the Slug/Snail family.[29] The expressions of Slug/Snail are positively correlated to increased cell migration and accumulation of β-catenin. These connections suggest that repression of cadherin expression also can suppress the signaling associated with β-catenin.

Recent studies have revealed that Lgr5, which originally discovered as Wnt target gene, regulates Wnt when binds to R-spondins (RSPO).[30] The Lgr5/R-spondin complex neutralizes Rnf43 and Znrf3, which are transmembrane E3 ligases that remove Wnt receptors.[31] The Rnf43 and Znrf3 are RING-type E3 ubiquitin ligases which function as tumor suppressors and found to be mutated in some colon cancer.[32] The overview of Wnt signaling pathway is summarized in Fig. 2.

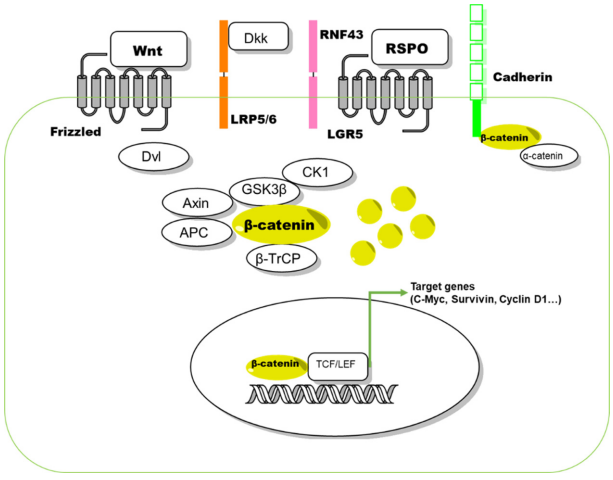


Fig. 2. Brief overview of Wnt signaling pathway.

Wnt in colon cancer

Although Wnt signaling plays a crucial role in regulating the stem cell maintenance and tissue homeostasis at the bottom of the intestinal crypt, hyperactivation of Wnt leads to development of colorectal cancer.[33] Therefore, components of Wnt signaling pathway are considered to be important therapeutic targets. The genetic mutations or overexpression of Wnt receptors contribute to the tumorigenesis in the colon. The most well-characterized common genetic mutations (~80%)

occur in colon cancer is APC mutation.[34] Since APC is a tumor suppressor which controls the degradation of β-catenin, the loss of APC function results in constitutive transcriptional activation of a TCF reporter gene and contributes to colon tumorigenesis.[35,36]

The overexpression of Axin2 is another biomarker of Wnt/β-catenin activation.[37] Upregulated expressions of Axin2/conductin mediates negative-feedback regulation of Wnt signaling and controls the levels of β-catenin.[38] Among several Wnt receptors, frizzled-7 (FZD7) activation is found in the canonical Wnt pathway and higher stage colon tumor tissues.[39] Downregulation of FZD7 using siRNA inhibited the cell growth and invasiveness of colon cancer cells.[39,40] These suggest that β-catenin, Axin2, and FZD7 are potential therapeutic targets in colon cancer.

Wnt in other cancers

The aberrant signaling of Wnt is also frequently found in several cancers such as hepatocellular carcinoma,[41] ovarian cancer,[42] melanoma,[43] and pancreatic cancer.[44] The expression of R-spondin1 is upregulated and causes drug resistance against chemotherapy in ovarian cancer cells.[45] The inhibition of R-spondin1 suppresses the growth and migration through Wnt/ β-catenin signaling in ovarian cancer cells.[45] High expression of β-catenin also enhances the self-renewal capacity of cancer stem cells in cancer cells including hepatocellular carcinoma.[46] Recently, it was found that the expression level of β-catenin is positively correlated with that of SIRT1, and they are prognostic biomarkers in hepatocellular carcinoma.[47] SIRT1 enhances the stability of β-catenin via deacetylation, and β-catenin accumulates in liver cancer stem cells which regulates tumorigenesis.[47] In addition, Wnt signaling is able to regulate epithelial-mesenchymal transition (EMT) and stemness in melanoma by degrading CD44/CTTN, and Wnt signaling is activated by down-regulated RNF128 expressions.[48]

Examples of natural products targeting Wnt signaling pathway

Natural products have been played an important role in the drug discovery and also employed in the elucidation of novel cellular mechanisms.[49] The genotypic screening

Table 1. List of natural products reported as Wnt inhibitors

	Compound	Source	Target gene	Type of cancer	Ref.
1	Apigenin	*Matricaria chamomilla*	β-catenin	Osteosarcoma	52
2	Bidebiline E	*Polyalthia cerasoides*	β-catenin/TCF	Colon cancer	53
3	Boehmenan	*Hibiscus ficulneus*	β-catenin	Colon cancer	54
4	Calotropin	*Calotropis gigantea*	CK1α	Colon cancer	55
5	Dalbinol	*Amorpha fruticosa*	β-TrCP	Hepatocellular carcinoma	56
6	Deguelin	*Mundulea sericea*	GSK-3β β-catenin	Triple-negative breast cancer	57
7	Esculetin	*Artemisia capillaris*	β-catenin/TCF Axin2	Colon cancer	58
8	Euphordraculoates B	*Euphorbia dracunculoides*	β-catenin/TCF Axin2	Colon cancer	59
9	Honokiol	*Magnolia officinalis*	GSK-3β β-catenin	Oral cancer	60
10	2-Hydroxycinnamaldehyde	*Cinnamomum cassia*	β-catenin/TCF	Colon cancer	61
11	Hydnocarpin	*Lonicera japonica*	Axin1,2 β-catenin/TCF	Colon cancer	62
12	Jatrophone	*Jatropha gossypiifolia*	WNT10B	Triple-negative breast cancer	63
13	Magnolol	*Magnolia obovata*	β-catenin/TCF	Colon cancer	64
14	Murrayafoline A	*Glycosmis stenocarpa*	Siah-1	Colon cancer	65
15	Periplocin	*Telectadium dongnaiense*	β-catenin/TCF	Colon cancer	66
16	Scopadulciol	*Scoparia dulcis*	β-catenin/TCF	Gastric cancer	67
17	Vicenin-2	*Ocimum sanctum*	GSK-3β β-catenin/TCF	Colon cancer	68
18	Xylogranin B	*Xylocarpus granatum*	β-catenin/TCF	Colon cancer	69

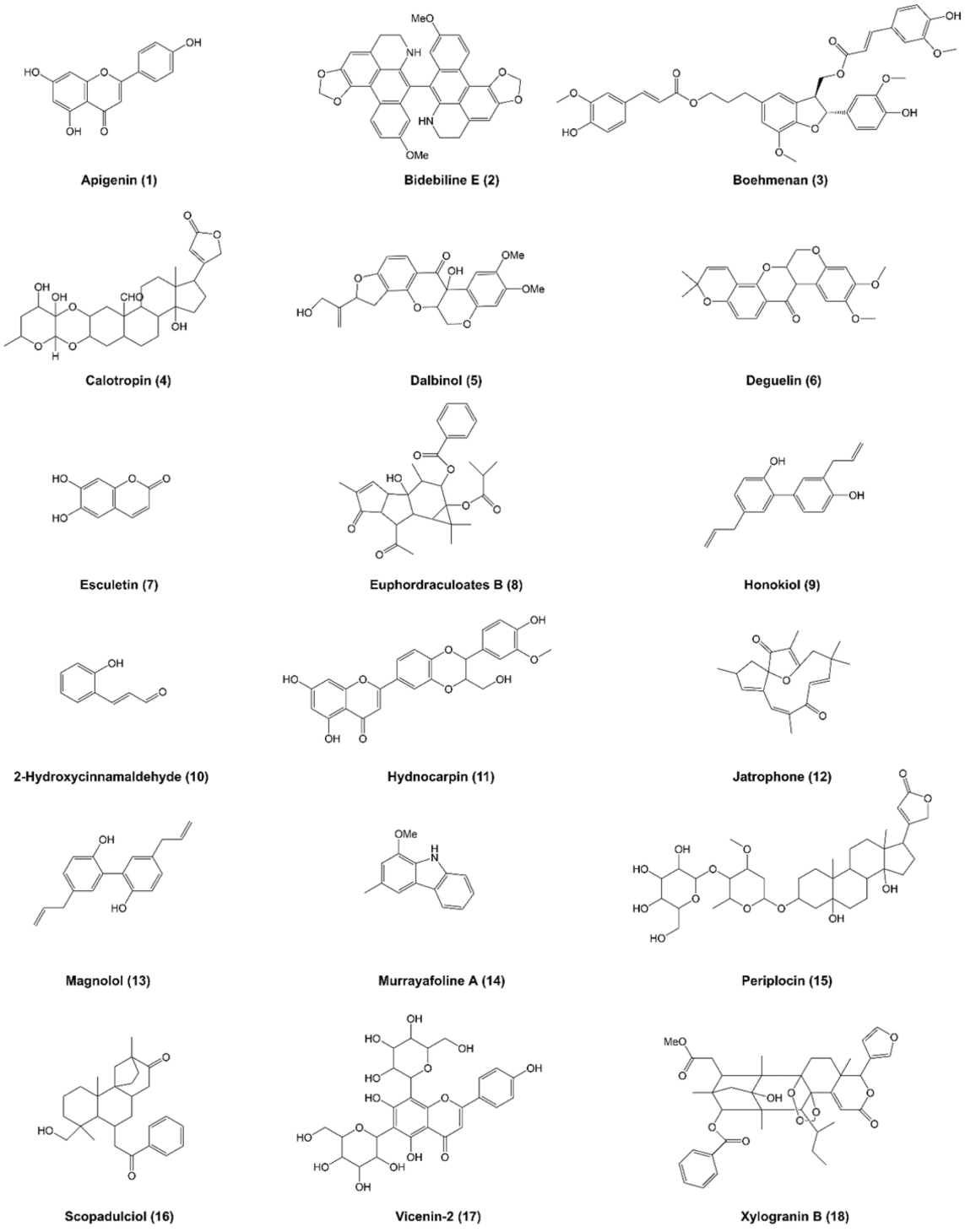


Fig. 3. The chemical structures of natural products-derived compounds reported as Wnt inhibitors.

is easy and efficient screening method to select effective compounds from the libraries of small molecules. One of the popular genotypic screening method to evaluate Wnt activity is TOPflash reporter gene assay, which evaluates the transcriptional activity of TCF/LEF by transfecting Wnt-associated vectors or using stable cell line which constitutively produces active Wnt signaling.[50,51] The results of TOPflash reporter gene assay only suggest whether the TCF/LEF transcription is inhibited. Using TOPflash reporter gene assay, many natural products have

been evaluated and elucidated for the Wnt inhibitory activity with various mode of actions. Herein, some of the natural products reported as Wnt inhibitors for cancer treatment are summarized. The chemical structures of compounds which were listed in Table 1 are depicted in Fig. 3.

Liu *et al.* reported that β-catenin is associated with the cell viability of osteosacrcoma cells, and application of apigenin, a flavonoid which is found in wide range of fruits and vegetables, suppressed the proliferation and invasion of osteosarcoma cells dependent on β-catenin expressions.[52] There are many other natural products that are reported as β-catenin inhibitor such as boehmenan (TOPflash IC_{50}: 1.9 μM),[54] bidebiline E (IC_{50}: 20.2 μM),[53] 2-hydroxycinnamaldehyde,[61] magnolol,[64] periplocin,[66] scopadulciol,[67] and xylogranin B.[69] Boehmenan, a component of stems of *Hibiscus ficulneus*, inhibited the translocation of β-catenin into the nucleus and decreased c-myc protein levels in colon cancer cells.[54] Similarly, Bidebiline E isolated from the root of *Polyalthia cerasoides* was shown to reduce the level of β-catenin and c-myc in colon cancer cells.[53] The antitumor activities of 2-hydroxycinnamaldehyde, a phenylpropanoid of the bark of *Cinnamomum cassia*, was assessed in human colon cancer cells. The Wnt target genes were suppressed by 2-hydroxycinnamaldehyde in both *in vitro* and *ex vivo* biochemical analysis.[61] Kang *et al.* demonstrated the underlying antiproliferation mechanism of magnolol, one of major compounds of the cortex of *Magnolia obovata,* in colon cancer cells by regulating Wnt signaling pathways. Magnolol significantly suppressed the proliferation of colon cancer cells *in vitro* and *in vivo* tumor growth by inhibiting the binding of β-catenin/TCF complexes and DNA promoters.[64] Bioactivity-guided fractionation of *Telectadium dongnaiense* led to the isolation of periplocin. Periplocin, a cardioglycoside, also exhibited potent anti-proliferative activity (IC_{50}: 0.06 μM) against human colon cancer cells via suppressing Wnt signaling pathway.[66] Scopadulciol, isolated by bioactivity-guided fractionation of *Scoparia dulcis*, induced the proteasome-dependent degradation of β-catenin in AGS human gastric adenocarcinoma cells.[67] In addition, scopadulciol in combination with TRAIL enhanced the apoptosis in TRAIL-resistant AGS cells. Using TOPflash assay, xylogranin B was identified as an active compound of *Xylocarpus granatum*.[69] Calotropin also regulates β-catenin degradation

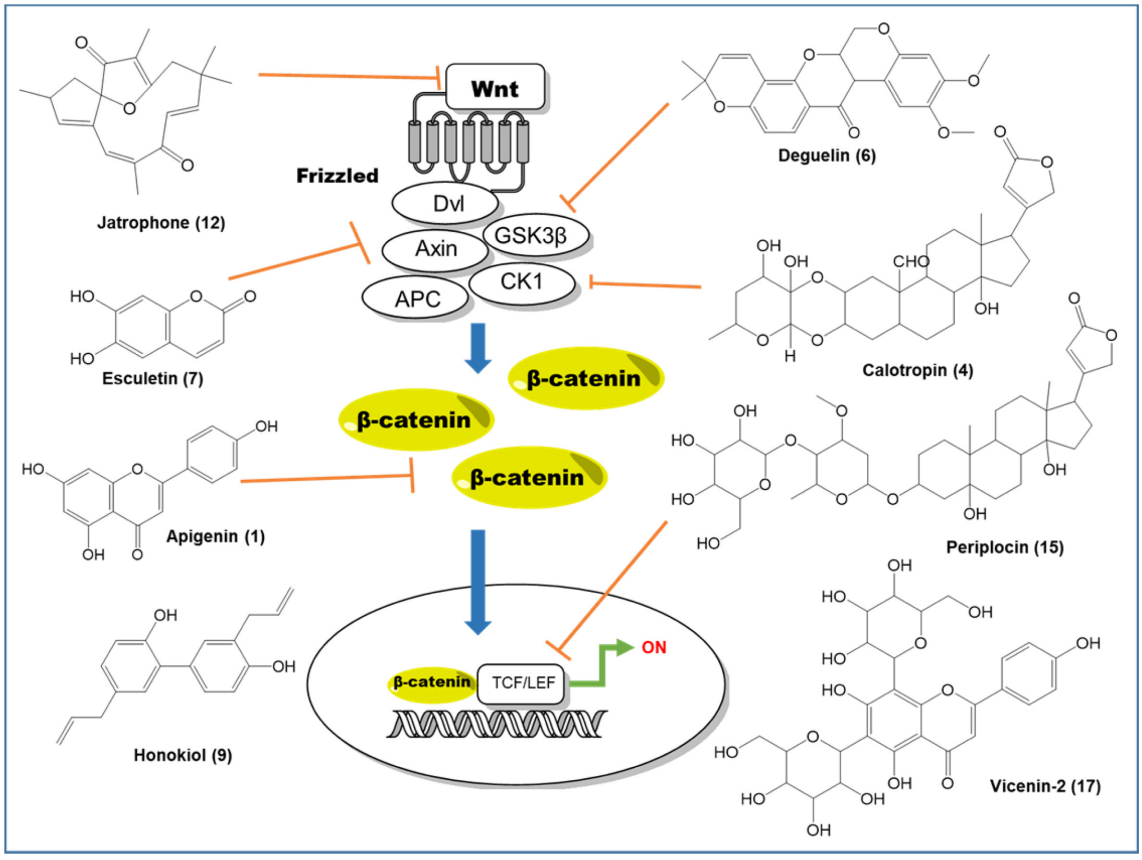


Fig. 4. Proposed mechanisms of action by natural products-derived Wnt inhibitors.

and exhibited a potent inhibitory activity in TOPflash assay with IC_{50} of 1.3 nM. Further mechanism study suggested that calotropin induces β-catenin degradation by upregulating CK1α expression which is a component of APC complex.[55] The β-TrCP also regulates β-catenin degradation via ubiquitination, and dalbinol was found to enhance the interaction between β-TrCP and β-catenin in hepatocellular carcinoma cells.[56] Another way to regulate β-catenin can be achieved by modulating phosphorylation of GSK3β. Several studies showed that deguelin,[57] honokiol,[60] or vicenin-2[68] activates GSK3β expression to induce β-catenin degradation. Interestingly, honokiol was able to induce apoptosis in oral squamous cell carcinoma with stem cell properties.[60] These findings suggest that targeting Wnt signaling also may regulate stem cell-like properties of cancer cells. The co-immunoprecipitation in colon cancer cells showed that β-catenin interacts with E-cadherin, which is an important epithelial-mesenchymal transition (EMT) biomarker. Esculetin inhibited the translocation of β-catenin via Axin2 suppression and E-cadherin upregulation mediated by GSK3β induced degradation of Snail1, which is a transcriptional repressor of *E-cadherin* promoter.[58] Euphordraculoates B and hydnocarpin also regulated β-catenin expression via Axin2 regulation.[59,62] The overexpression of Wnt10B expression was observed in metastatic breast cancer cells, and jatrophone inhibited Wnt signaling and target genes such as AXIN2, MYC, PCNA, CCND1, and HMGA1 by regulating WNT10B.[63] Murrayafoline A exhibited β-catenin degradation activity mediated by upregulation of phosphorylated Siah-1, an E3 ubiquitin ligase, in colon cancer cells.[65] The proposed mechanism of action for the natural products-derived Wnt inhibitors was depicted in Fig. 4.

Structure-activity relationship studies of natural product derivatives targeting Wnt signaling pathway

Synthesis of bioactive natural product derivatives and

Table 2. Examples of SAR studies of natural products and their derivatives

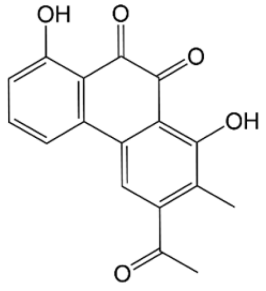
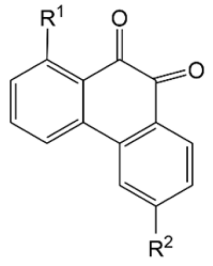
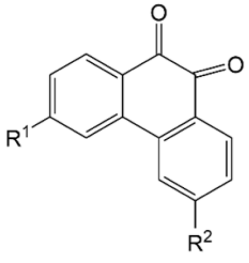
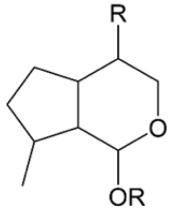
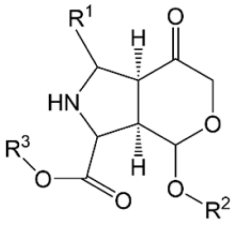
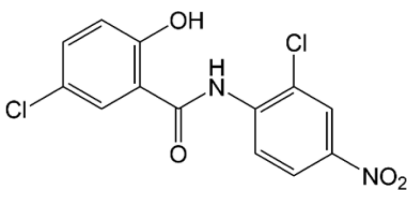
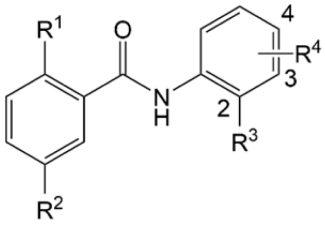
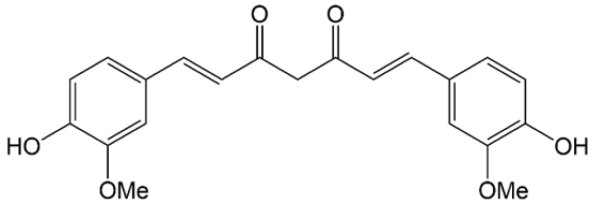
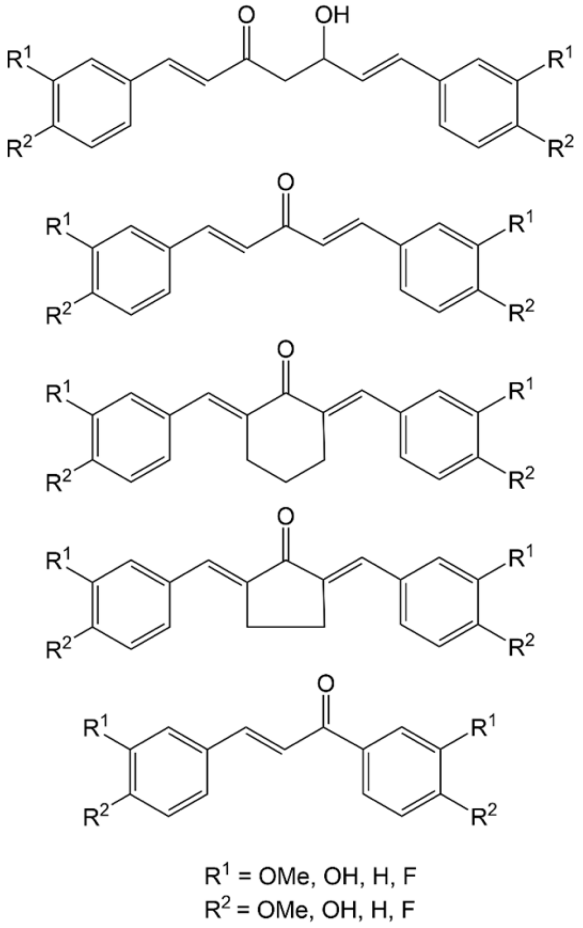
Natural Product	Structure	Derivatives
Haloquinone		  RFC (R^1= OMe, R^2=OMe) RFC-HY (R^1= OH, R^2=OH) RFE (R^1= OH, R^2=OMe) RFD (R^1= OMe, R^2=OMe) RFD-HY (R^1= OH, R^2=OH)
Iridoids		 R^1 = (Het)Ar R^2 = Ac, Bz, Piv, $COCH_2OME$, $COCH_2OPh$, 3-methylbutanoyl, 4-pentenoyl, 2-furanoyl, Me. allyl R^3 = Me, allyl, Bn, *t*Bu
Niclosamide		 R^1 = OH, H, OMe R^2 = Cl, Br, H, Ph R^3 = Cl, H, OMe, Br, O-PEG-N_3 R^4 = 2-NO_2, 3-NO_2, 4-NO_2, 4-NH_2, 4-N_3, 4-CO_2H, 4-CN, 4-NHAc

Table 2. continued

Natural Product	Structure	Derivatives
Curcumin		

analysis of structure-activity relationship (SAR) are also very important process in drug discovery program. Examples of natural products and selected analogues are summarized in Table 2. For example, haloquinone was initially isolated from *Streptomyces venezuelae* sp. *xanthophaeus* and was shown as an effective antibiotic agent against halobacteria.[70] Due to the ease of total synthesis of haloquinone, Halbdel *et al*. designed a series of novel derivatives of haloquinone and evaluated their biological activities using TOPflash assay, and compound RFD was most potent in β-catenin inhibition (IC_{50} not determined).[71] However, none of the derivatives was more potent than haloquinone. The findings indicated that symmetric ring structures compared to the substituents at the aromatic rings are more important for Wnt pathway inhibition. Iridoids are group of cyclopentan-(c)-pyran monoterpenoids that are found in a large number of botanical resources and also *Iridomyrmex*, a genus of ants.[72] Takayama *et al*. synthesized collections of iridoids-inspired compounds and investigated their bioactivity using HEK293 reporter cell line stimulated by Wnt3a.[73] The SAR analysis suggested that R^2 group is important for Wnt pathway inhibition activity. The bulky carboxylic residues in R^2 group decreased their Wnt inhibitory activities, whereas compounds with acetic acid ester in R^2 position generally showed potent Wnt inhibition activity. From the large screening of FDA-approved drugs using Frizzled1-GFP stable cell line (Fzd1GFP-U2OS), niclosamide that is used for intestinal tapeworm infections was selected as the most potent agent for Frizzled1 receptor internalization.[74] Mook *et al*. designed derivatives of niclosamide and evaluated the activity using the same Frizzeled-GFP stable cell line.[75] Although niclosamide itself showed the most potent activity for Frizzled internalization and inhibition of β-catenin transcription, the SAR data suggested that the substitution of the nitro

group at R^4 with amine or acetamide dramatically decreased the inhibitory activity in TOPflash assay. Interestingly, the substitution of nitro group at R^4 with an aryl sulfonamide resulted in increased β-catenin transcription activity. Curcumin, a component of *Curcuma longa*, has been studied widely for variety of biological activities including anticancer activity.[76] It is reported that curcumin inhibits the growth of colon cancer cells and tumor by regulating Wnt/β-catenin pathway.[77] Leow *et al*. synthesized five series of curcumin analogs and determined the Wnt inhibitory activity using TOPflash and further examined the mechanism of selected analogs in osteosarcoma cells.[78] Reduction in the flexibility of the intermediate linker and electron donating group ring substituents enhanced the Wnt inhibitory activity.

Future directions

Many efforts have been made to discover safe and efficient Wnt inhibitors to treat cancer. However, it is challenged by the multiple side effects of targeting Wnt.[79] Therefore, it is important to find an alternative way to target Wnt signaling pathway instead of directly targeting β-catenin. Understanding exactly which FZDs are involved in specific diseases and finding specific FZDs regulator may reduce the possibility of side effects. Natural products are very attractive sources in the discovery of small molecules targeting Wnt signaling because many natural products were reported as Wnt inhibitors without further in detailed mechanism studies. Employing these natural products, it is anticipated to find an alternative target that modulates Wnt signaling pathways beyond an on-target toxicity.

Acknowledgments

This study was supported by a grant from the National Research Foundation of Korea (NRF) funded by the Korean Government (NRF-2016M3A9B6902986).

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Received February 11, 2019
Revised June 12, 2020
Accepted June 14, 2020