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Review Article

Regulating WNT Pathway by Natural Compounds

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ABSTRACT

This review currently focused on WNT, originates from wg, which means wingless and Ing denotes genes, having complicated network of ten homologous Frizzeled receptors (FzD), RYK (Receptor Like Tyrosine Kinase), Retinoic acid-related Orphan Receptors (RoR), Protein Tyrosine Kinase 7 (PTK7), Muscle Specific tyrosine Kinase (MuSK), co-receptors, Lipoprotein Receptor-related Protein (LRP5/6) and 19 cysteine rich glycolipoproteinswnt ligands. It is highly recommended pathways for the process of angiogenesis, embroyonic development by maintaining proliferation and differentiation. Most of the research is going in to know about cancer therapy or treatment by WNT pathways down regulation *via* canonical β-catenin dependent/ T-Cell Factor (TCF) pathway and non-canonical β-catenin pathway. It is much needed way for developing the targeted therapies opposite to cancers, which involves phosphoryalation by Glycogen Synthase Kinase-3 (GSK-3) protein complex. In addition, there are some natural compounds which shows WNT pathway inhibitors. According to recent studies, Triple Negative Breast Cancer (TNBC) depends on WNT-pathway but no drugs are currently under clinical trials, it requires high cost in discovery and is a time consuming process. It clearly shows emergency for such type of drugs in cancer therapy.

Keywords: WNT, Cancer, GSK-3 protein, Natural products, TNBC, Receptors

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INTRODUCTION

WNT is originated from the *Wg* (wingless) and *Int* genes. Recessive mutations in the *Wg* genes affect wing development in *Drosophila.* Wnt is a family consists of 19 proteins and cysteine-rich glycoproteins. Wnt ligands activate several signaling pathways involved in the regulation of development at different stages (Zhang B and Ma JX, 2010).

Wnt pathway also plays an important role in angiogenesis. The Wnt pathway is one of the most important signaling cascades in the early events of embryonic development, where it controls cell proliferation and differentiation (Nusse R, 2005; Komiya Y and Habas R, 2008). Till date, the Wnt signaling is still not completely understood. This is mainly because it is it is a complicated network of ten G Protein Coupled Receptors (GPCR), homologue FZD receptors (Schulte G, 2015), Ryk, ROR, PTK, MuSK (Roy L and Dahl KDC, 2018), the co-receptors LRP5/6 (MacDonald BT and He X, 2012), and 19 glycolipoprotein Wnt ligands (Miller JR, 2001). There is a high degree of promiscuity in the ligand-receptor interactions, although certain Wnt have higher affinities to certain FZD receptors and co-receptors. To communicate, the cells engage with chemical signals, which, when received by the recipient cells, trigger defined intracellular signaling pathways in order to relay the information and provide the adequate response to the external stimuli. This enables the body to coordinate patterning and organ development during embryogenesis, to keep the organism in homeostasis and to respond to external stresses and inputs, and to regenerate after injury. On the cellular level, a signaling cascade is initiated by secreted ligands (e.g., hormones, cytokines, neurotransmitters, growth factors) produced by one cell, which then bind to a receptor on another cell. The receptors in most cases are located on the cell surface, and the signal is then relayed through intracellular components of the pathway, called transducers and second messengers, resulting in the corresponding cellular effect, for example target gene transcription or changes in an enzymatic activity (Uings IJ and Farrow SN, 2000; Shaw HV, *et al*., 2019). Aberrant Wnt signaling underlies cancerous transformation and growth in many tissues, such as the colon, breast, liver, and others. Down regulation of the Wnt pathway is a desired mode of development of targeted therapies against these cancers. Wnt signaling is one of the essential pathways involved in animal embryonic development, during which it has numerous roles including the regulation of cell proliferation and differentiation In the healthy adult tissues however, it is largely inactive, with some exceptions such as the renewal of the gastro-intestinal tract as well as haematopoiesis and regeneration after injury It is to no surprise then that aberrant activation of this pathway can lead to diseases of neoplastic nature such as cancer (Nusse R, 2005; Krausova M and Korinek V, 2014; Malhotra S and Kincade PW, 2009; Whyte JL, *et al*., 2012; Polakis P, 2012).

The canonical Wnt signaling pathway is the most studied and well-characterized in various diseases including cancer, cardiovascular diseases and ocular diseases. Wnt operates either through canonical or non-canonical pathways which are differentiated by beta-catenin involvement (Shi J, *et al*., 2016). Wnt signaling is generally divided into three distinct branches-

- Canonical β-catenin dependent/TCF pathway
- Non-canonical β-catenin/TCF pathway/β-catenin independent

LITERATURE REVIEW

Canonical Wnt pathway

This is the common Wnt signaling pathway which is initiated by Wnt ligands. When the Wnt ligands are not present, then β-catenin a transcription factor, which act as a down-stream effector of this Wnt pathway, is begin to phosphorylate by a protein complex which contains GSK-3 in the cell cytosol and is keep on degrading to prevent its accumulation (*Figure 1*).

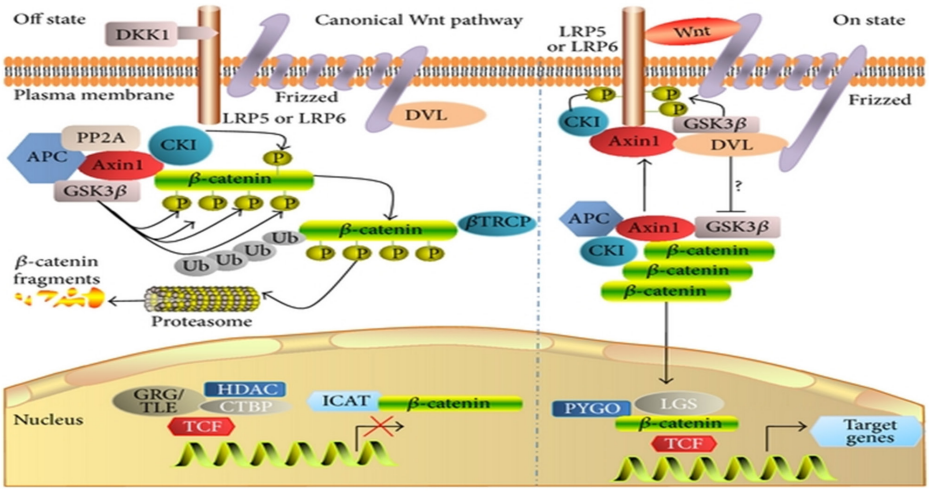

Figure 1: Canonical signaling Wnt pathway (Shi J, *et al*., 2016)

Non-canonical Wnt pathway

The non-canonical Wnt pathway is an unconventional pathway, comprises of several easily distinguishable branches and is also associated with some other activities which are independent of conventional Wnt/β-catenin signaling (*Figure 2*). The Wnt/PCP pathway regulates orientation of cellular structure. This pathway is further subdivided into two ways, which are

- Planar Cell Polarity (PCP) pathway and
- Ca^{2+} pathway

Wnt inhibitory factor 1

Wnt Inhibitory factor 1 is Wnt pathway inhibitor, it get binds to Wnt ligands, similar. It was discovered back in 1999, where it was found to inhibit the somitogenesis in the development of *Xenopus* embryo, and it was also interacted with *Drosophila* Wingless and *Xenopus* Wnt (Uings IJ and Farrow SN, 2000). Although the *WIF1* doesn't found to share the CRD sequence neither with Fz or sFRPs, but however, it has a highly conserved WIF Domain (WD) which is an N-terminal domain, that contains 150 amino acids and it also contains a hydrophilic domain at C terminus with 45 amino acids, along with five Epidermal Growth Factor (EGF). The prostate, breast, lung and bladder cancers were directly correlated with the downregulated expression levels of *WIF1* (*Figure 3*).

Wnt/β-catenin signaling: A therapeutic mechanism

Wnt/B-catenin signaling is activated by WNTs-a family of lipoglycoproteins, out of which 19 can be found in humans and by the fact the production, secretion and diffusion of them, through tissues is tightly controlled (Solis GP, *et al*., 2013). Just by binding to the FZD family of GPCRs (Koval A and Katanaev VL, 2011; Schulte G, 2015) (ten homologues in humans), and depending on the ligand-receptor combination and cellular context Wnt pathways can be activated. The most common of them is the PCP branch which is mostly involved in cytoskeleton rearrangement, cell polarity and migration; another one is Wnt/Ca^{2+} branch which promote proliferation and known to antagonize the canonical pathway; and then finally the so-called canonical branch (Komiya Y and Habas R, 2008) (*Table 1*).

DISCUSSION

Existing drugs and natural compounds: As Wnt pathway inhibitors

Natural Products (NPs) have been acting as a direct source of therapeutic agents and as a basis for drug development from many years as of now. Given are the natural compounds and drugs that are being used as inhibitors of Wnt pathway.

Vitamins: Retinoid which is used for cancer therapy (notably acute promyelocticleukemia) and chemoprevention, is synthesized from vitamin A from our body. Chemo preventive effects were seen in animal models with colorectal and breast cancers by an active form of vitamin D1α, 25-dihydroxyvitamin D3, and its synthetic derivatives. Earlier the mechanism of vitamins inhibiting Wnt/β-catenin pathway was unknown later it was suggested that activated nuclear receptors for vitamins interact with β-catenin and compete with TCFs also. It's also found that both vitamin A and D might activate Wnt/β-catenin inhibitory proteins. E.g. Disabled 2 (Dab2) with the help of retinoic acid (Park CH, *et al*., 2005) (*Table 2*).

Polyphenols: Polyphenols are a group of chemicals found in plants, characterized by the presence of more than one phenol unit or building block per molecule. Several polyphenols, such as quercetin, Epigallocatechin3-Gallate (EGCG), curcumin, and resveratrol have been implicated as inhibitors of Wnt/β-catenin signaling pathway, although the mechanisms of action of these agents are not clear due to their inherent lack of specificity and inhibitory effects on multiple pathways (Kim J, *et al*., 2006; Rao CV, *et al*., 1995; Jaiswal AS, *et al*., 2002; Roccaro AM, *et al*., 2008; Morris HR, *et al*., 1987; Takahashi-Yanaga F, *et al*., 2003). The Differentiation-Inducing Factors (DIF) first identified in Dictyosteliumdiscoideum as putative morphogens required for stalk cell differentiation, also have a phenol unit and strongly inhibit the proliferation of human cancer cells. It has been reported that DIF-1 and DIF-3 inhibit the Wnt/β-catenin signaling pathway through the activation of GSK-3β (Yasmin T, *et al*., 2005; Mori J, *et al*., 2005; Takahashi-Yanaga F, *et al*., 2006). Apart from β-catenin, GSK-3β has many target proteins such as glycogen synthase, Tau, CREB, and AP-1. Cyclin D1, a known oncogene, is also one of target molecules of GSK-3β, and phosphorylation by GSK-3β triggers cyclin D1 degradation (Sherr CJ, *et al*., 1996; Diehl JA, *et al*., 1998; Takahashi-Yanaga F, Sasaguri T, 2008). Because activators of GSK-3β, such as DIFs, could reduce cyclin D1 mRNA and protein levels, they may be applicable for the treatment of cancer and other proliferative disorders (Trosset JY, *et al*., 2006).

Curcumin: Natural derivatives of curcumin also inhibited the Wnt/β-catenin pathway, but it is through downregulation of p300, one of the transcriptional coactivators (Ryu MJ, *et al*., 2008). These studies suggest that the Wnt-antagonizing activity of curcumin can contribute to its anti-cancer and anti-angiogenesis effects (Conney AH, *et al*., 1991; Park CH, *et al*., 2005).

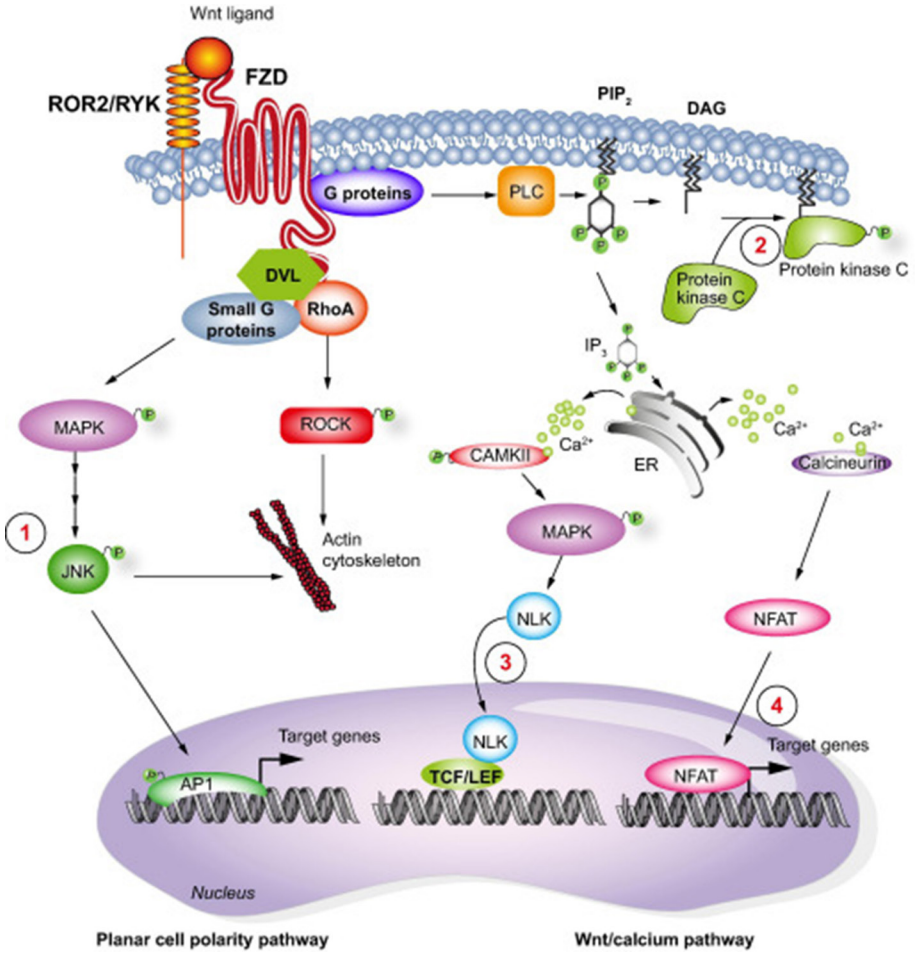

Figure 2: Non-canonical signaling pathway

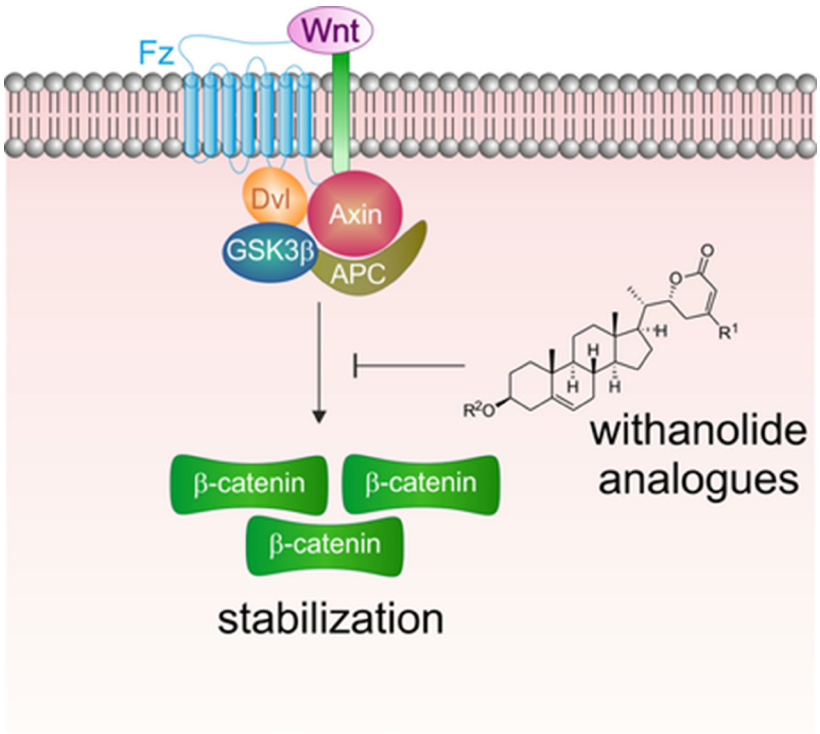

Figure 3: Withanolide analogues in Wnt/β-catenin signaling pathway

Table 1: Target genes of the Wnt/β-catenin signaling pathway

Targeted gene	Diseases
Tiam1	Colon tumors
WNT5A	Leukemia
MITF	Melanomas
Tcf-1	Human colon cancer
LEF-1	Human colon cancer
Apc	CRC
Axin	Several cancers
MMP 2/9	T cells
Endothelin 1 *(END1)*	Human colon cancer
AXIN2	Human cancer, tooth agenesis

Table 2: Summary of inhibitors against Wnt signaling pathway

Inhibitors	Subcategory	Therapeutic medication
Small molecules	Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Aspirin, Sulindac, Celecoxib
Existing drugs and natural compound	• Vitamins • Polyphenols	Retinoids, 1 α 25,-dihydroxy-Vitamin D3 Querucetin, EGCG Curcumin, Resveratrol, DIF

Querucetin: Quercetin inhibited the transcriptional activity of beta-catenin/Tcf in SW480 and also in HEK293 cells transiently transfected with constitutively active mutant beta-catenin gene, whose product is not induced to be degraded by APC-Axin-GSK3beta complex, so it was concluded that its inhibitory mechanism was related to beta-catenin itself or downstream components. Quercetin is an excellent inhibitor of beta-catenin/Tcf signaling in SW480 cell lines, and the reduced beta-catenin/Tcf transcriptional activity is due to the decreased nuclear beta-catenin and Tcf-4 proteins (Srivastava NS and Srivastava RA, 2019).

Epigallocatechin-3-gallate (EGCG): EGCG, which is the major polyphenolic constituent in green tea, attenuates Wnt pathway. EGCG on gastric cancer remain unclear. We found that EGCG significantly inhibited proliferation and increased apoptosis of SGC-7901 cells *in vitro* Wnt/beta-catenin signaling in response to EGCG treatment of SW480 colon cancer cells, which show constitutively active Wnt pathway due to APC mutation. These cells were transfected with pTOPflash (beta-catenin/Tcf4 responsive reporter gene). 3h after transfection, cells were treated with increasing concentrations of EGCG. The pTOPflash luciferase activity was measured 24 h later and our results showed that Wnt/beta-catenin signaling was decreased in a dose dependent manner. Further pathway components through which EGCG inhibits the pathway, we transfected HEK293 cells, in which Wnt pathway is highly regulated, with mutant beta-catenin and pTOPflash (Yang C, *et al*., 2016; Ruonan Z and Wargovich M, 2007).

Resveratrol: Resveratrol, a dietary polyphenol, that has been shown to possess potent antioxidant as well as anti-inflammatory properties, mediates induction of antioxidant enzymes and modulates lipid metabolism while attenuating hepatic lipid peroxidation. The decreased nuclear localization of β-catenin by resveratrol treatment could be due to reduced expression of lgs and pygoI, which are regulators of β-catenin localization, showing significantly decrease the level of β-catenin in the nucleus of colon cancer cells (Frémont L, 2000; Hope C, *et al*., 2008).

Withanolides: Withanolide are the natural products extracted by using a pregnenolone-derived-lactone as the key intermediate that was transformed into a lactone appended to the D-ring of the steroidal scaffold. Only few clinical drug candidates that target Wnt signaling are available so far, and new small-molecule modulators of Wnt-related processes are in high demand. Dysregulation of Wnt signaling is linked to various diseases. This natural product-inspired compound library contained potent inhibitors of Wnt signaling .Synthesis inspired by the natural product withanolide has yielded a potent inhibitor of the Wnt/β-catenin signaling pathway that acts by elevating Axin protein levels in a tankyrase-independent manner (Sheremet M, *et al*., 2017; Logan CY and Nusse R, 2004).

Jerusalem artichoke (Helianthus tuberosus): According to a study, the plant extract of Jerusalem was obtained using a special water extraction technology which is done under mild temperature conditions. This technology is one of its kind as it allows the extracting compound to be obtained in its natural state unlike the ethanol extraction method. The obtained extract was found to inhibit the Wnt pathway, and which was also reported to be confirmed by the beta-catenin stabilization assay, which is known to serve as an independent standard for the measurement of Wnt pathway activity (Logan CY and Nusse R, 2004).

Ampelopsis japonica: Extract of *Ampelopsis japonica* (a far Eastern plant) also found to inhibit Wnt pathway in both GFP and luciferase assays, as proved by some studies.

Jatrophone: Structurally Jatrophone is a macrocyclicditerpene. It has a unique oxaspiro core along with electrophilic centers. It was isolated from the *Jatropha isabelli* and *Jatropha gossypiifolia,* plants that belongs to the family Euphorbiacea. Along with its unique structure Jatrophone also displays many of biological properties, such as it is known to be anti-tumorous, cytotoxic, anti-inflammatory, anti-malarial and fungicidal. As soon we look into its Mechanism of Action (MOA), one can found that JA block the Wnt/β-catenin signaling somewhere between the receptor and β-catenin activation. It could also serve as a lead candidate molecule for development of anti-breast cancer agent for the management of disease in patients diagnosed with highly chemo-resistant metastatic TNBC (Logan CY and Nusse R, 2004; Fatima I, *et al*., 2017; Ling T, 2015).

FUTURE SCOPE

According to the recent studies, along with various signaling pathways, Wnt inhibiting pathway is receiving great attention predominately, and the study of these pathways for their integral role in ocular diseases is or will be promising orientation in the field of research. As there are many known WNT-dependent cancers that exists, such as TNBC, with unmet medical needs which clearly indicates the future of drugs against these cancers, that

they are in the first row to get the Food and Drug Administration (FDA) approval.

CONCLUSION

Wnt signaling is one of the developmental pathways, whose reactivation in many adult tissues underlies oncogenic transformation. As per the reports no drugs inhibiting the Wnt pathways are present in the current market and they are not even under process of any advanced clinical trials, so this clearly defines that the demand for such drugs is urgent. Targeting a selected pathway is hindered by several obstacles, with such complexed pathology in a multifactorial disease like cancer. As what have seen, the traditional drug discovery process has become a costly and time-consuming practice that is why massive improvement is still required upon developing a therapeutic intervention which is efficient enough for targeting Wnt signaling in tumors.

REFERENCES

1. Zhang B, Ma JX. Wnt pathway antagonists and angiogenesis. Protein Cell. 2010; 1(10): 898-906.
2. Nusse R. Wnt signaling in disease and in development. Cell Res. 2005; 15(1): 28-32.
3. Komiya Y, Habas R. Wnt signal transduction pathways. Organogenesis. 2008; 4(2): 68-75.
4. Schulte G. Frizzleds and WNT/β-catenin signaling-the black box of ligand-receptor selectivity, complex stoichiometry and activation kinetics. Eur J Pharmacol. 2015; 763: 191-195.
5. Roy L, Dahl KDC. Can stemness and chemoresistance be therapeutically targeted *via* signaling pathways in ovarian cancer? Cancers. 2018; 10(8): 241.
6. MacDonald BT, He X. Frizzled and LRP5/6 receptors for Wnt/β-catenin signaling. Cold Spring Harb Perspect Biol. 2012; 4(12): a007880.
7. Miller JR. The wnts. Genome Biol. 2001; 3: 1-5.
8. Uings IJ, Farrow SN. Cell receptors and cell signalling. Mol Pathol. 2000; 53(6): 295.
9. Shaw HV, Koval A, Katanaev VL. Targeting the Wnt signalling pathway in cancer: Prospects and perils. Swiss Med Wkly. 2019; 149(3940): w20129.
10. Krausova M, Korinek V. Wnt signaling in adult intestinal stem cells and cancer. Cell Signal. 2014; 26(3): 570-579.
11. Malhotra S, Kincade PW. Wnt-related molecules and signaling pathway equilibrium in hematopoiesis. Cell Stem Cell. 2009; 4(1): 27-36.
12. Whyte JL, Smith AA, Helms JA. Wnt signaling and injury repair. Cold Spring Harb Perspect Biol. 2012; 4(8): a008078.
13. Polakis P. Drugging Wnt signalling in cancer. EMBO J. 2012; 31(12): 2737-2746.
14. Shi J, Chi S, Xue J, Yang J, Li F, Liu X. Emerging role and therapeutic implication of Wnt signaling pathways in autoimmune diseases. J Immunol Res. 2016.
15. Solis GP, Lüchtenborg AM, Katanaev VL. Wnt secretion and gradient formation. Int J Mol Sci. 2013; 14(3): 5130-5145.
16. Koval A, Katanaev VL. Wnt3a stimulation elicits G-protein-coupled receptor properties of mammalian frizzled proteins. Biochem J. 2011; 433(3): 435-440.
17. Park CH, Chang JY, Hahm ER, Park S, Kim HK, Yang CH. Quercetin, a potent inhibitor against β-catenin/Tcf signaling in SW480 colon cancer cells. Biochem Biophys Res Commun. 2005; 328(1): 227-234.
18. Kim J, Zhang X, Rieger-Christ KM, Summerhayes IC, Wazer DE, Paulson KE, *et al.* Suppression of Wnt signaling by the green tea compound (-)-epigallocatechin 3-gallate (EGCG) in invasive breast cancer cells: Requirement of the transcriptional repressor HBP1. J Biol Chem. 2006; 281(16): 10865-10875.
19. Rao CV, Desai D, Rivenson A, Simi B, Amin S, Reddy BS. Chemoprevention of colon carcinogenesis by phenylethyl-3-methylcaffeate. Cancer Res. 1995; 55(11): 2310-2315.
20. Jaiswal AS, Marlow BP, Gupta N, Narayan S. β-catenin-mediated transactivation and cell–cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells. Oncogene. 2002; 21(55): 8414-8427.
21. Roccaro AM, Leleu X, Sacco A, Moreau AS, Hatjiharissi E, Jia X, *et al.* Resveratrol exerts antiproliferative activity and induces apoptosis in Waldenstrom's macroglobulinemia. Clin Cancer Res. 2008; 14(6): 1849-1858.
22. Morris HR, Taylor GW, Masento MS, Jermyn KA, Kay RR. Chemical structure of the morphogen differentiation inducing factor from *Dictyostelium discoideum*. Nature. 1987; 328(6133): 811-814.
23. Takahashi-Yanaga F, Taba Y, Miwa Y, Kubohara Y, Watanabe Y, Hirata M, *et al. Dictyostelium* differentiation-inducing factor-3 activates glycogen synthase kinase-3β and degrades cyclin D1 in mammalian cells. J Biol Chem. 2003; 278(11): 9663-9670.
24. Yasmin T, Takahashi-Yanaga F, Mori J, Miwa Y, Hirata M, Watanabe Y, *et al.* Differentiation-inducing factor-1 suppresses gene expression of cyclin D1 in tumor cells. Cancer Sci. 2005; 338(2): 903-909.
25. Mori J, Takahashi-Yanaga F, Miwa Y, Watanabe Y, Hirata M, Morimoto S, *et al.* Differentiation-inducing factor-1 induces cyclin D1 degradation through the phosphorylation of Thr286 in squamous cell carcinoma. Exp Cell Res. 2005; 310(2): 426-433.
26. Takahashi-Yanaga F, Mori J, Matsuzaki E, Watanabe Y, Hirata M, Miwa Y, *et al.* Involvement of GSK-3β and DYRK1B in differentiation-inducing factor-3-induced phosphorylation of cyclin D1 in HeLa cells. J Biol Chem. 2006; 281(50): 38489-38497.
27. Sherr CJ. Cancer cell cycles. Science. 1996; 274(5293): 1672-1677.
28. Diehl JA, Cheng M, Roussel MF, Sherr CJ. Glycogen synthase kinase-3β regulates cyclin D1 proteolysis and subcellular localization. Genes Dev. 1998; 12(22): 3499-3511.
29. Takahashi-Yanaga F, Sasaguri T. GSK-3β regulates cyclin D1 expression: A new target for chemotherapy. Cell Signal. 2008; 20(4): 581-589.
30. Trosset JY, Dalvit C, Knapp S, Fasolini M, Veronesi M, Mantegani S, *et al.* Inhibition of protein-protein interactions: The discovery of drug like β-catenin inhibitors by combining virtual and biophysical screening. Proteins. 2006; 64(1): 60-67.
31. Ryu MJ, Cho M, Song JY, Yun YS, Choi IW, Kim DE, *et al.* Natural derivatives of curcumin attenuate the Wnt/β-catenin pathway through down-regulation of the transcriptional coactivator p300. Biochem Biophys Res Commun. 2008; 377(4): 1304-1308.
32. Conney AH, Lysz T, Ferraro T, Abidi TF, Manchand PS, Laskin JD, *et al.* Inhibitory effect of curcumin and some related dietary compounds on tumor promotion and arachidonic acid metabolism in mouse skin. Adv Enzyme Regul. 1991; 31: 385-396.
33. Park CH, Hahm ER, Park S, Kim HK, Yang CH. The inhibitory mechanism of curcumin and its derivative against β-catenin/Tcf signaling. FEBS Lett. 2005; 579(13): 2965-2971.

34. Srivastava NS, Srivastava RA. Curcumin and quercetin synergistically inhibit cancer cell proliferation in multiple cancer cells and modulate Wnt/β-catenin signaling and apoptotic pathways in A375 cells. Phytomedicine. 2019; 52: 117-128.
35. Yang C, Du W, Yang D. Inhibition of green tea polyphenol EGCG ((−)-epigallocatechin-3-gallate) on the proliferation of gastric cancer cells by suppressing canonical wnt/β-catenin signalling pathway. Int J Food Sci Nutr. 2016; 67(7): 818-827.
36. Ruonan Z, Wargovich M. Mechanisms of inhibition of Wnt/beta-caternin pathway by (-)-epigallocatechin-3-gallate. Cancer Res. 2007; 67(9_Supplement): 1328.
37. Frémont L. Biological effects of resveratrol. Life Sci. 2000; 66(8): 663-673.
38. Hope C, Planutis K, Planutiene M, Moyer MP, Johal KS, Woo J, *et al*. Low concentrations of resveratrol inhibit Wnt signal throughput in colon-derived cells: Implications for colon cancer prevention. Mol Nutr Food Res. 2008; 52(S1): S52-S61.
39. Sheremet M, Kapoor S, Schröder P, Kumar K, Ziegler S, Waldmann H. Small molecules inspired by the natural product withanolides as potent inhibitors of wnt signaling. Chembiochem. 2017; 18(18): 1797-7806.
40. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004; 20: 781-810.
41. Fatima I, El-Ayachi I, Taotao L, Lillo MA, Krutilina R, Seagroves TN, *et al*. The natural compound Jatrophone interferes with Wnt/β-catenin signaling and inhibits proliferation and EMT in human triple-negative breast cancer. PLoS One. 2017; 12(12): e0189864.
42. Ling T, Hadi V, Guiguemde A, Landfear SM, Rivas F. *Jatropha* natural products as potential therapeutic leads. The formation, structure and activity of phytochemicals. 2015.