Modulation of Wnt/β-catenin signaling pathway by bioactive food components

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The Wnt/β-catenin signaling pathway, one of the most conserved intercellular signaling cascade, is a known regulator of cellular functions related to tumor initiation and progression, cell proliferation, differentiation, survival and adhesion. Because aberrant Wnt/β-catenin signaling has been observed in a variety of human cancers including a majority of colorectal cancers, about half of prostate cancers and a third of melanomas, inhibitors of its complex signaling pathways are being investigated for therapy as well as chemoprevention of these cancers. During the last decade, several naturally occurring dietary agents have been shown to target intermediates in the Wnt/β-catenin signaling pathway. In this review, we highlight the current understanding of the Wnt/β-catenin signaling pathway and present an analysis of the key findings from laboratory studies on the effects of a panel of dietary agents against a variety of cancers. Promise of these agents for treating and preventing human cancer is then discussed.

Introduction

The term ‘Wnt’ was coined by the amalgamation of Drosophila segment polarity gene Wingless (1) and the mouse proto-oncogene Int-1 (2,3). Wnt signaling pathway is known as a key regulator of a variety of cellular processes (4,5). It is also known that aberrant Wnt signaling pathway occurs in a variety of cancers, including a third of melanomas and a majority of colorectal cancers (5–7). Many studies have repeatedly demonstrated that bioactive food components present in fruits, vegetables and spices exhibit cancer chemopreventive effects in variety of preclinical models (8–16) and thus, these have drawn a great deal of attention owing to their ability to suppress cancers (17). Accumulating research evidence suggests that many dietary factors may be used alone or in combination with traditional chemotherapeutic agents to prevent the occurrence of cancer, their metastatic spread or even to treat cancer. Because Wnt is considered to play an important role in development and progression of cancer(s), which in turn are recognized to be moderated by dietary agents, in this review, we will discuss various dietary agents that have been shown to serve as antagonists of the Wnt/β-catenin signaling pathway.

Abbreviations: APC, adenomatous polyposis coli; CRC, Colorectal cancer; CSC, cancer stem cell; EGCG, epigallocatechin-3-gallate; GSK-3β, glycogen synthase kinase-3β; HCC, hepatocellular carcinoma; Lef, lymphoid enhancer-binding factor; LRP, LDL receptor related protein; MITF, microphthalmia-associated transcription factor; NF-κB, nuclear factor-kappa B; SFN, Sulforaphane; Tcf, T-cell factor.

These authors contributed equally to this work.

Fig. 1. Wnt/β-catenin signaling pathway.
Wnt/beta-catenin signaling in cancer

Mutations that result in Wnt/beta-catenin signaling pathway being constitutively active lead to cancer. Axin2 also known as axin-like protein (Axil) or axis inhibition protein 2 (Axin2) or conductin is a protein that in humans is encoded by the Axin2 gene. Axin2 apparently plays an important role in the regulation of the stability of beta-catenin in the Wnt signaling pathway and is known to display a predisposition to colon cancer (40). Familial adenomatous polyposis is an inherited disorder in which patients display numerous polyps in the colon and rectum. Truncations in APC, which promotes aberrant activation of Wnt/beta-catenin signaling pathway leading to adenomatous lesions, are the most frequent cause of familial adenomatous polyposis (59–62). Mutations in beta-catenin and APC have been observed in a variety of other tumors (4,5,63), suggesting that deregulation of Wnt/beta-catenin signaling is an important event in the genesis of many cancers. In fact, aberrant Wnt/beta-catenin signaling is an important event in the genesis of many cancers. In an important role in the regulation of the stability of nuclear beta-catenin was found to be detectable soon after loss of APC (64). Several studies observed that stabilizing mutations in beta-catenin in the absence of mutations in APC in ~7% of sporadic human colon carcinomas and thus, these studies provide additional genetic evidence linking APC loss and beta-catenin activation (49,64–66). Furthermore, transgenic mice with stabilized mutant beta-catenin develop numerous intestinal adenomas (64,67). Taken together, these studies suggest that dysregulation of beta-catenin is a key oncogenic event that follows loss of APC.

beta-Catenin mutations and interstitial deletions have been reported in both primary hepatocellular carcinomas (HCC) and hepatoma cell lines (68–70). Ser 37 mutation was rarely observed in HCC but alterations affecting the putative phosphorylation residues were common.

Studies suggest that 50% of HCC that develop in transgenic mice expressing c-myc or H-ras in the liver contain beta-catenin mutations, indicating that beta-catenin activation can cooperate with ras or myc in progression of HCC (69,70). Forty-eight percent of sporadic hepatoblastomas, a type of childhood malignant liver tumors, exhibit beta-catenin mutations and exon 3 deletions (71). Wilms tumor, a common childhood renal cancer, has been shown to harbor mutations in beta-catenin. An interesting finding in these studies was that 90% of these tumors have beta-catenin mutation at codon 45 (72–74).

Wnt/beta-catenin signaling in melanomas. A single amino acid substitution at the N-terminus of beta-catenin was identified as a melanoma-specific antigen (75) and this sequence is part of a sequence recognized by a melanoma-specific tumor-infiltrating lymphocyte. This study was the first to suggest a mutation in beta-catenin could result in cancer. Abnormally high levels of beta-catenin have been observed in a subset of melanomas and are usually associated with mutation in CTNNB1 (50). beta-catenin mutations were reported to occur at Ser 37, a residue rarely reported in colon cancer (50), 76. However, similar to colon cancer, overexpression of APC reduced the levels of beta-catenin in these lines (50). Studies suggest that deregulation of Wnt signaling may ultimately lead to deregulation of microphthalmia-associated transcription factor-M (MITF-M) expression resulting in improper cell functions (differentiation, proliferation and survival) (6,77). MITF is essential for melanocyte differentiation and its heterozygous mutations cause auditory–pigmentary syndromes. Functional cooperation of MITF with Lef1 results in synergistic transactivation of an early melanoblast marker dopachrome tautomerase gene promoter (24). Lef1 also interacts with PAX3 and Groucho-related corepressor Grg4 in melanocytes. During active Wnt/beta-catenin signaling, Grg4 and PAX3 are removed from the dopachrome tautomerase gene promoter and no longer interact with Lef1 thus resulting in a loss of PAX3-mediated repression (78). Another factor that has been implicated in the control of proliferation and strongly upregulated in melanomas is the POU domain transcription factor Brm-2 (79–81). In melanoma cells, down-regulation of Brm-2 is associated with changes in morphology and loss of melanocytic and neural crest markers, like MITF and tyrosinase (81). A decrease in the production of Brm-2 is associated with a loss of tumorigenicity of these cells in nude mice (79). An active Lef1/Tcf-binding site has been identified in the Brm-2 promoter (81), implying that Wnt/beta-catenin signaling can induce BRN-2 protein, which is involved in cell proliferation and another protein (MITF) that is involved in cell differentiation.

Wnt/beta-catenin signaling in colorectal cancer. Colorectal cancer (CRC) is the third most common cause of cancer death in the USA (64,82). One of the central players, in the series of molecule changes resulting in CRC, is APC which was identified as the responsible germline mutation in familial adenomatous polyposis patients (62,83). Eighty percent of non-inherited CRC cases carry mutations in APC, an important component in the Wnt/beta-catenin signaling pathway. Since mutations in CRC occur at the early stages of colorectal cancers, studies suggest that 42% of CRC contain APC mutations. Deletion of APC is significant because it is often accompanied by mutations in beta-catenin. The BRAF mutation at codon 600 occurs in 25% of colorectal cancers (82). Wnt/beta-catenin signaling can induce BRN-2 protein, which is involved in cell proliferation and another protein (MITF) that is involved in cell differentiation.
cancer, it means the functional loss of APC is a prerequisite for further progression toward malignancy (84). Reintroduction of wild-type APC results in decreased levels of β-catenin. Studies suggest that transfection of APC in colon cancer cells reduces the abnormally high Tcf reporter plasmid activity (85). Interestingly, rare cell lines without APC mutations also displayed β-catenin/Tcf transcriptional activity as measured by luciferase reporter assay (49). Sequencing the β-catenin gene (CTNNB1) in two APC−/−β-catenin activated cell lines revealed mutations at the GSK-3β consensus phosphorylation site of β-catenin: a deletion of Ser 45 in HCT116 cell line and a Ser 55 to Thr substitution in SW-48 cells. Expression of β-catenin stability leads to a dominant effect on Tcf/β-catenin transcription (49). Mutations in β-catenin gene have been observed in ~50% of CRCs without APC mutations, representing <10% of overall CRCs. These mutations occur mainly in the microsatellite-stable tumors (65,86). Immunolocalization of β-catenin in colon carcinomas showed a strong nuclear enrichment at the invasion front, whereas in large parts of the central tumor area, β-catenin was detected in the cytoplasm and at the membrane, indicating that high levels of nuclear β-catenin play a role in the transition to the invasive state of tumor cells (87–89).

**Wnt/β-catenin signaling in prostate cancer**

Prostate cancer is one of the few cancers where the aberrant Wnt/β-catenin signaling appears to be a late event in tumorigenesis. Approximately a third of prostate tumors have aberrant Wnt/β-catenin signaling (90). Mutations in APC, β-catenin and β-TrCP have been detected in prostate cancer (90–92). A study using single-strand conformation polymorphism in a panel of 104 prostate cancers identified five mutations in the regulatory site of β-catenin (91). Four of these sites affected putative phosphorylation sites of β-catenin and one affected a residue adjacent to Ser 33, similar to those seen in colon cancer (65). The expression levels of Wnt ligands (Wnt 1, Wnt 2 and Wnt 5a) were positively correlated with Gleason scores as well as to the cellular level of β-catenin and serum prostate specific antigen levels (93–95). Studies by Truica et al. (96) have demonstrated that β-catenin interacts with androgen receptor and enhances the transcriptional activity for androgen receptor in LNCaP cells suggesting a possible mechanism of cross talk between Wnt and androgen signaling pathways. Several other studies using yeast two-hybrid, in vitro and in vivo protein binding assays, have confirmed the interaction between Wnt and androgen receptor signaling pathways (93,97,98).

**Wnt/β-catenin signaling in other diseases**

Misregulation of Wnt/β-catenin signaling pathway leads to a variety of abnormalities. A mutation in LRP receptor related protein has been identified that leads to increased bone density at defined locations, such as the jaw and palate (99,100). A single amino acid substitution makes LRP5 insensitive to the inhibition of Wnt signaling (99,101). Frame shift and missense mutations in LRP5 resulted in loss of function in LRP5 ultimately leading to decreased bone mass (102). Mutations in LRP5 and Fz4 receptor (FZD4) result in defective vasculogenesis in the LR5-driven vasculogenesis in the peripheral retina (osteoarthritis–pseudoglioma syndrome and familial exudative vitreopathy) (58,103–105). Mutations in other components of Wnt signaling pathway produce dramatic effects, such as disturbances in skeletal bone mass or cancer (reviewed in detail by Clevers in ref. 63). Germline mutations in the Wnt pathway cause several hereditary diseases, and somatic mutations are associated with cancer of the intestine and a variety of other tissues (63). Mutation in Axin2 results in oligodontia (severe tooth agenesis), a condition in which multiple permanent teeth are missing (40).

**Role of Wnt signaling in cancer stem cells**

Wnt signaling, besides performing vital role in embryonic development, is also thought to play key role in the biology of cancer stem cells (CSCs) and acquisition of epithelial to mesenchymal transition phenotype of the cells (106–109). A study demonstrated the importance of canonical Wnt signaling in mediating development of early hematopoietic progenitors during human development (106). In this study, several complementary methods were used to demonstrate that canonical Wnt signaling is important for development of human embryonic stem cells-derived cells with both hematopoietic and endothelial potential. Wnt/β-catenin signaling is known to be required for neural differentiation of embryonic stem cells (110) and outcome decision in neural crest stem cells (111). Canonical Wnt signaling is believed to play an important role in the maintenance of hematopoietic progenitors and also in the lineage commitment of progenitors during hematopoiesis (107). Survivin, which is a Wnt/cyclic adenosine monophosphate response element-binding protein/β-catenin-regulated gene, is important during hematopoiesis and is prominently upregulated in CD34+ hematopoietic stem and progenitor cells upon growth factor treatment.

Recent studies are beginning to show the use of chemopreventive agents in targeting CSCs. Sulforaphane (SFN), a natural agent found in cruciferous vegetables such as broccoli, has been reported to inhibit the growth of breast CSCs in vitro and in vivo through inhibition of Wnt-regulated self-renewal (112). Preclinical and epidemiological data suggest the role of vitamin D in exerting antiproliferative and prodifferentiating effects on a variety of stem and progenitor cells (113,114). Genistein has been reported to act synergistically with a vitamin D derivative to inhibit the growth of prostate cells and regulate genes that are involved in stem cells renewal (115–117). A recent study by Kakarla et al. (118) showed that curcumin inhibits Wnt/β-catenin signaling in mammary stem cells by inhibiting their self-renewal capability. Another study by Yu et al. (119) showed that curcumin in combination with the therapeutic cocktail of leucovorin, 5-fluorouracil and oxaliplatin (FOLFOX) eliminated colon CSC population suggesting that curcumin by itself or together with the conventional chemotherapeutic could be an effective treatment strategy for preventing the emergence of chemoresistant colon cancer cells by reducing/eliminating CSCs.

**Naturally occurring compounds targeting Wnt/β-catenin signaling**

Naturally occurring compounds represent attractive candidates for development as chemopreventive agents. Naturally occurring dietary agents circumvent the need to introduce foreign compounds into healthy asymptomatic individuals. Dietary agents are also in general less toxic, more accessible and less expensive than synthetic agents. In the past few years, several laboratories have identified numerous phytochemicals that have useful biological properties; however, only few groups have directly evaluated the ability of these agents to disrupt β-catenin-mediated Wnt signaling. Flavanoids (genistein), curcumin, epigallocatechin-3-gallate (EGCG), resveratrol, luteolin, retinoids, lycopene, deguelin and SFN are been described here.

**Flavonoids**

The flavonoids comprise a large class of low-molecular weight natural products of plant origin ubiquitously distributed in foods. They are recognized as dietary constituents having a variety of biological effects among which there are some that have been associated with protective activity in the development of degenerative diseases, such as atherosclerosis or cancer (120–123). Several studies suggest that an intake of flavonoids results in reduced cancer risk (17,124,125). Genistein, an important isoflavone, is found in a number of plants, such as soybeans and soy products like tofu. Kaempferol and iso-rhamnetin are also important flavones found in broccoli. Studies by Park et al. (120) indicate that β-catenin/Tcf-driven transcription was suppressed strongly by flavanone in AGS gastric cancer cells dose dependently. Studies by Sarkar et al. (126) suggest that isoflavone (notably genistein) upregulated the expression of GSK-3β, enhanced GSK-3β binding to β-catenin and increased β-catenin phosphorylation, suggesting that genistein could inactivate Wnt/β-catenin signaling thereby inhibiting prostate cancer growth (126,127). Genistein
also diminished Wnt 1-induced proliferation and decreased the expression of Wnt targets viz. c-myc and cyclin D1 (127–129).

**Curcumin**
Curcumin or diferuloylmethane [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], a yellow pigment, is a major component of turmeric and a member of the ginger Curcuma longa (Zingiberaceae). Turmeric has been used in ayurvedic medicine in India for several thousands of years (130). The therapeutic benefits of curcumin have been reported as an analgesic, antiinflammatory, antibacterial, antiviral, antiparasitic, antioxidant, antiarthritic, antihypercholesterolemic and antihypertensive (131–133). Its anti-inflammatory activity is used in the treatment of a variety of diseases ranging from asthma (by down-regulating hyaluronidase activity) to Alzheimer’s disease (reducing expression of β-amyloid) and human immunodeficiency virus (17,134–136). Dietary curcumin has been shown to prevent cancer in the skin, forestomach, duodenum and colon in mice and the tongue, colon, mammary and sebaceous glands in rats (137,138). Furthermore, curcumin has also been associated with regression of established malignancy in humans (17,127,139–141). Curcumin specifically inhibits the expression of cyclooxygenase-2, which plays an important role in colon carcinogenesis (130,142). Studies suggest that curcumin is not toxic to humans up to a dose of 8000 mg/day when taken orally for 3 months, suggesting a biological effect in the area of chemoprevention (130). Curcumin treatment inhibits the messenger RNA expression of Wnt target genes c-myc, c-fos, c-jun and iNOS in a variety of cancer cells (143,144). Studies suggest that curcumin treatment resulted in a dose-dependent decrease in β-catenin transcriptional activity in a variety of CRC cell lines (145,146). Curcumin treatment (40 μM dose) resulted in the increased degradation of cytoplasmic β-catenin and decreased nuclear β-catenin levels (146). Studies by Ryu et al. (146) also demonstrate a dose-dependent decrease in expression of nuclear p300 coactivator upon curcumin treatment. This is especially significant since nuclear β-catenin forms a complex with Tcf4 and p300 coactivator to generate a transcriptional active complex (147).

**EGCG and green tea polyphenols**
Tea, derived from the plant *Camellia sinensis*, is the most popular beverage consumed by two-thirds of the world’s population (17). Green, black and oolong tea are the main commercial types and these differ in how they are processed and fermented. Green tea contains epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin-3-gallate and epicatechin. These compounds grouped as catechins are strong radical scavengers and metal chelators in a number of in vivo and chemical-based assays (148). An increasing number of studies have also demonstrated these antioxidative effects in vivo. Studies have shown that tea treatment can induce Phase II metabolism and antioxidant enzymes in both animal models and humans (85,149–151). Several studies have shown that the effect of EGCG and other tea polyphenols on key cell signaling pathways may be dependent on polyphenol-mediated reactive oxygen species. Green tea was found to inhibit the formation of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine-induced colon aberrant crypts in the rat as well as intestinal polyps in the APC-Min mouse (152,153). Decrease in tumor burden was associated with downregulation of β-catenin expression in the intestines as well as markedly lowered expression of β-catenin/Tcf target genes (c-jun and cyclin D1). These findings are important because they suggest the possibility for intervention by tea against the early stages of human CRC, involving the β-catenin/APC pathway and the alteration of Wnt target genes (65,85,151). Studies suggest that β-catenin/Tcf4 transcriptional activity was inhibited in a concentration-dependent fashion upon treatment with EGCG (154) in HEK293 cells induced with β-catenin/Tcf4 (154). Wnt/β-catenin signaling was found to be inhibited by EGCG in a dose-dependent manner in breast cancer cells. Treatment with EGCG resulted in upregulation of HMG-box containing protein 1, an important antagonist of Wnt signaling (127,155). EGCG reduced both proliferation and invasiveness of breast cancer cells through induction of HMG-box containing protein 1 and the subsequent downregulation of Wnt/β-catenin signaling.

**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 (156–158). It has been shown that resveratrol increases hepatic glutathione content, scavenges free radicals and induces enzymes of phase II hepatic metabolism. It also inhibits the transcription factor nuclear factor-kappa B (NF-kB), which induces the inflammatory cascade (158–160). Resveratrol has been shown to reduce the nuclear translocation of NF-kB (161) as well as interfere with its transcription (162). Additionally, resveratrol also produces a significant reduction in the expression of several proinflammatory cytokines (156,162). Studies suggest that resveratrol inhibits skin tumorigenesis through the regulation of phosphatidylinositol-3-kinase and Akt proteins, which have been implicated in development and progression of cancer (127,163). Resveratrol has shown to significantly decrease the level of β-catenin in the nucleus of colon cancer cells. The decreased nuclear localization of β-catenin by resveratrol treatment could be due to reduced expression of Igs and pygol, which are regulators of β-catenin localization (164). In addition to the solid tumor, resveratrol also inhibits proliferation and induced cell cycle arrest and apoptosis in Waldenstrom’s macroglobulinemia cells. These effects of resveratrol were found to be mediated via the downregulation of Akt, mitogen-activated protein kinase and Wnt signaling pathways (165). Several studies suggest that resveratrol-induced apoptosis is associated with the activation of the p53 in a dose- and time-dependent manner (127,165). Resveratrol also modulates DNA double-strand break repair pathways in p53-dependent manner (166), suggesting the regulatory effect of resveratrol on p53 signaling.

**Lupeol**
Lupeol is a well-studied dietary triterpene. Lupeol (C29H40O) has a melting point of 215–216°C and a molecular weight of 426. It is found in several fruits (olives, figs, mangoes, strawberries and grapes), vegetables (green peppers, white cabbage and tomato) and medicinal plants (American ginseng, Shea butter plant, Taraxacum officinale, Crataeva nurvala and Bombax ceiba). Lupeol was used extensively by native tribes of North America, China, Africa and the Caribbean islands (167). Lupeol has been shown to exhibit various pharmacological activities under in vitro and in vivo conditions. These include its beneficial activity against inflammation, cancer, arthritis, diabetes, heart diseases, renal toxicity and hepatic toxicity (reviewed in ref. 167–185). It is noteworthy to mention that lupeol exhibits strong anti-mutagenic activity under in vitro and in vivo systems (179,186). Studies by Nigam et al. (179) have demonstrated that application of lupeol (200 μg per mouse) prevents 7,14-dimethylbenz(a)anthracene-induced DNA damage (DNA strand breaks) in mouse skin. Recently, lupeol was shown to inhibit benzo-a-pyrene genotoxicity in a mouse model (180). In benzo-a-pyrene-treated animals, a significant induction of chromosomal aberration and micronuclei was recorded, with a decrease in mitotic index, and significant decrease in benzo-a-pyrene-induced clastogenicity was recorded upon lupeol administration (180). It has demonstrated that lupeol inhibits tumor promotion in a murine mouse model of the skin (181). Topical administration of lupeol (40 mg per animal per thrice a week) was shown to significantly decrease tumor burden in mice (181). The antitumor effects of lupeol were observed to be associated with its potential to modulate NF-kB and phosphatidylinositol-3-kinase/Akt pathway which play an important role in tumor progression. Our laboratory has studied the beneficial effects of lupeol in a variety of cancers, such as prostate, pancreas and melanoma (182–184,187,188). A recent study suggested that lupeol caused inhibition in the growth and proliferation of human prostate cancer cells irrespective of their androgen status (187). Recent studies from our laboratory have suggested the inhibition of human metastatic melanoma cells in vitro and in a xenograft mouse model (182).
laboratory has also demonstrated that lupeol has a significant growth inhibitory potential on melanoma cells that exhibit constitutive Wnt/β-catenin signaling (189). We have also demonstrated that lupeol inhibits the localization of β-catenin into the nucleus and decreases the phosphorylation status of β-catenin at important serine sites (ser 552 and ser 675). Recent studies suggest that phosphorylation of β-catenin at Ser-552 or Ser-675 abets β-catenin to localize to the nucleus and induce transcription of various downstream targets (190–192).

Retinoids

Vitamin A is converted in vivo to a number of different metabolites collectively referred to as retinoids. Retinoids are potent regulators of cell proliferation and differentiation that are applicable to cancer therapy and prevention (193,194). The use of retinoids as an important chemopreventive agent has been highlighted by several in vitro studies: preclinical animal model experiments, epidemiologic evidence and clinical trials (195). Retinoids have been shown to inhibit the function of the oncogenic AP-1 and Wnt/β-catenin signaling pathways as well as stabilize components of adherens junctions (196). GSK-3β, an important component of the Wnt/β-catenin signaling pathway, plays a key role in retinoid-induced degradation of cyclin D1. In human bronchial epithelial cells, mutation of Thr286 made cyclin D1 resistant to retinoid treatment and pharmacological inhibitors of GSK-3β antagonized the effect of retinoids (193,197).

Other natural products

Lycopene is a bioactive red-colored pigment naturally occurring in plants. Interest in lycopene is increasing due to increasing evidence proving its preventive properties toward numerous diseases. In vitro, in vivo and ex vivo studies have demonstrated that lycopene-rich foods are inversely associated to diseases, such as cancers, cardiovascular diseases, diabetes and others (198–200). Experimental studies have shown that lycopene inhibits cell growth in breast, prostate and endometrial cancer cells with regulation of cell cycle-related genes (201,202). The inhibition of NF-kB DNA-binding activity by lycopene was mediated through the downregulation of IkB phosphorylation, NF-kB expression and NF-kB p65 subunit translocation from cytosol to nucleus (203). Studies suggest that the consumption of lycopene is inversely related to human prostate cancer risk (127). Lycopene reduced localization of β-catenin in the nucleus perhaps by attenuating the effects of GSK-3β phosphorylation (109).

Deguelin is a rotenoid from Mandulea sericea (Family: Leguminosae). This agent has shown great potential as a chemopreventive and therapeutic agent against several types of cancers, including colon, lung and breast (204–209). Deguelin induces apoptotic death by downregulating cell survival pathways, including Akt, mitogen-activated protein kinase and surviving in a variety of human breast cancer cells (206). Research studies suggest that deguelin has been shown to suppress hypoxia-inducible factor-1α/heat shock protein 90 interaction and expression in radioresistant lung cancer cells (204,210).

SFN is an isothiocyanate that is abundantly present in cruciferous vegetables like broccoli and cauliflower. SFN has been found to inhibit carcinogen-induced mammary gland tumorigenesis (211), colonic aberrant crypt foci (212,213), stomach tumors (214) and lung cancer (215) in rats/mice. Several animal model studies suggest that SFN can inhibit carcinogenesis (211,212,216). A study by Hu et al. (217) suggests that ApcMin/+ mice fed with SFN-supplemented diet developed significantly fewer and smaller polyps.

Summary

Aberrant Wnt/β-catenin signaling is observed in a variety of cancers and plays an important role in cancer progression. The data from in vitro, in vivo and preclinical human studies highlight the importance of natural products that exert their inhibitory effects on carcinogenesis and cancer progression by downregulating Wnt/β-catenin signaling pathway. We believe that these natural products that are non-toxic in nature could be used either alone or in combination with conventional therapeutics for the prevention and/or treatment of a variety of human malignancies. Appropriate and relevant animal model studies along with novel clinical trials are needed to fully appreciate the value of these and other natural products for improving the quality of human health.

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