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Natural products against renin-angiotensin system for antifibrosis therapy

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Review

Small molecules from natural products targeting the Wnt/β-catenin pathway as a therapeutic strategy

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ABSTRACT

The Wnt/β-catenin signaling pathway is an evolutionarily conserved developmental signaling event that plays a critical role in regulating tissue development and maintaining homeostasis, the dysregulation of which contributes to various diseases. Natural products have been widely recognized as a treasure trove of novel drug discovery for millennia, and many clinical drugs are derived from natural small molecules. Mounting evidence has demonstrated that many natural small molecules could inhibit the Wnt/β-catenin pathway, while the efficacy of natural products remains to be determined. Therefore, this paper primarily reviews the targeting mechanism of natural small molecules for aberrant Wnt/β-catenin pathway that is intimately implicated in the pathogenesis of myriad diseases, such as cancers, renal diseases, neurodegenerative diseases and bone disorders. In addition, this review also highlights some natural products that have the potential to halt Wnt/β-catenin pathway, especially for porcupine, the receptors of Wnt ligands, β-catenin and β-catenin-dependent proteins. Additionally, a series of natural small molecules have shown good therapeutic effects against mutations of the Wnt/β-catenin pathway, which may dramatically facilitate the development of natural products in Wnt/β-catenin pathway intervention.

1. Introduction

The Wnt/β-catenin signaling pathway is an evolutionarily conserved cellular signaling cascade that plays prominent roles in various biological processes and the pathogenesis of numerous diseases, such as the early embryonic development as well as organogenesis and adult tissue homeostasis [1]. The Wnt/β-catenin pathway primarily consists of the canonical Wnt/β-catenin signaling (β-catenin/T cell factor (TCF)-dependent interaction) and non-canonical Wnt/β-catenin signaling (β-catenin/TCF-independent interaction) [2]. Canonical Wnt/β-catenin signaling includes Wnt ligand secretion, Wnt/receptors interaction, β-catenin stabilization and translocation [3,4]. Although the Wnt/β-catenin pathway shows many benefits, its dysregulation causes extensive diseases, such as cancer, cardiovascular disease and renal disease [5–9]. Many biological antibodies and chemotherapeutic reagents targeting the aberrant Wnt/β-catenin signaling have been developed, some of which are in different clinical trials [9–17]. However, side effects and resistance of biological antibodies as well as chemotherapeutic reagents are frequently observed in clinical trials, which severely restrict their use.

Natural products have been widely used for the treatment of various cancers, cardiovascular diseases and renal diseases for many years [18–20]. It was reported that 46% of drugs approved by food and drug administration are derived from natural small molecules from 1981 to 2014 [21]. Reportedly, many natural small molecules from natural products have many effective pharmacological activities, including anti-cancer, anti-bacterial, anti-fibrotic and anti-oxidant activities, which fueling considerable enthusiam for natural products as a source of pharmaceutical exploitation [19,22–29]. As thus, we posited that targeting the Wnt/β-catenin pathway with natural small molecules may

Abbreviations: APC, adenomatous polyposis coli; Axin, axis inhibition protein; AKT, protein kinase B; β-TrCP, β-transducin repeats containing protein; BPA, bisphenol A; c-Myc, cellular homologue of myelocytomatosis viral oncogene; CK1, casein kinase 1; Cyclin D1, cell cycle regulator D1; CKD, chronic kidney disease; Dkk, dickkopf; FZD, Frizzled; GSK3β, glycogen synthase kinase 3β; HCT, human colon cancer tissue; LRPs, low-density lipoprotein receptor-related proteins; LEF, lymphoid enhancing factor; PC, *Poria cocos*; RNF43, ring finger protein 43; ROR2, receptor tyrosine kinase-like orphan receptor 2; R-Spondin, roof plate-specific spondin; Runx2, runt-related transcription factor 2; TCF, T cell factor; TGF-β1, transforming growth factor β1; TNBC, triple-negative breast cancer

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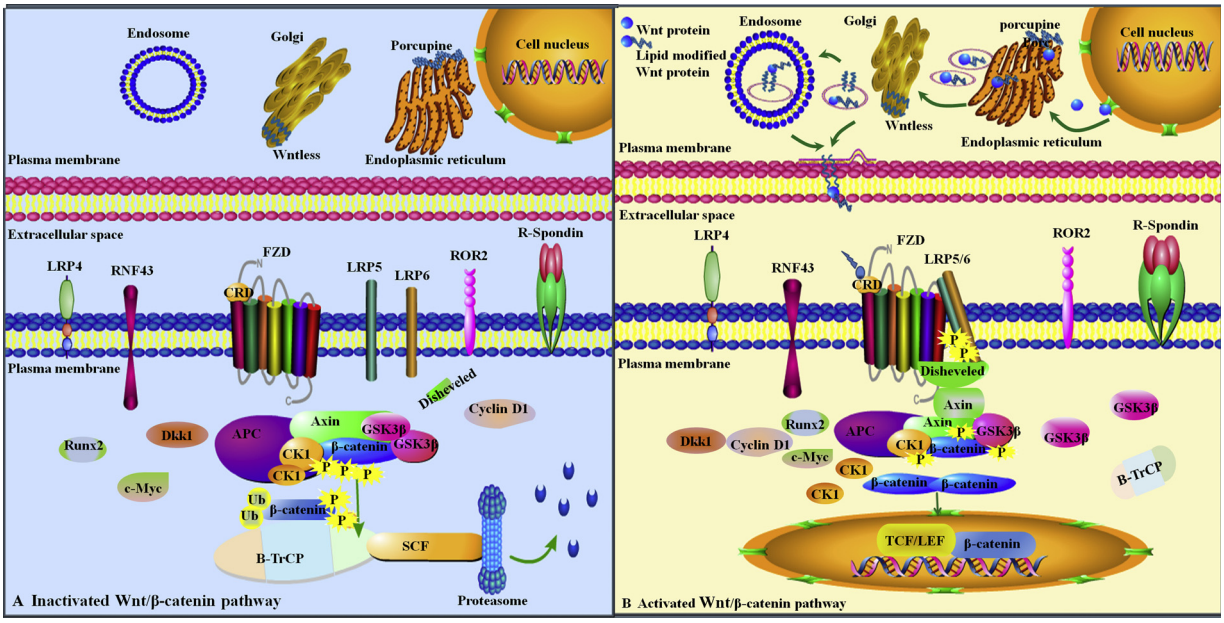

Fig. 1. Inactivated and activated Wnt/β-catenin signaling. (A) Inactivated Wnt/β-catenin signals. The destruction complex in the cytoplasm mainly consists of CK1, GSK3β, Axin, APC, protein phosphatase 2A, and β-TrCP. When Wnt is absent, CK1 and GSK3β phosphorylate β-catenin. The β-TrCP ubiquitinate phosphorylated β-catenin, and the latter is finally degraded by the proteasome. β-TrCP is a protein included in F-box. SCF is a complex of Skp, Cullin and F-box. (B) Activated Wnt signaling. In the presence of Wnts, Wnt proteins are lipidated by the porcupine in the endoplasmic reticulum, modified by Wntless in Golgi and ultimately transported to the plasma membrane for secretion. The binding of lipidated Wnts leads to the formation of a receptor complex, FZD and LRP5/6, which promotes the recruitment of Dishevelled to the receptor complex and the phosphorylation of LRP5/6. The Axin interacts with phosphorylated LRP5/6 and the destruction complex takes apart, which protects β-catenin from degradation. Stabilized β-catenin subsequently binds TCF in the nucleus of cells to regulate target genes.

be an effective therapy for identifying promising drug candidates. In this review, we primarily describe the Wnt/β-catenin signaling pathway in the development of multiple diseases such as cancer, renal disease, neurodegenerative disease and bone disorder. Additionally, the underlying mechanisms of small natural products that regulate the Wnt/β-catenin pathway are also highlighted.

2. The Wnt/β-catenin signaling pathway

2.1. Canonical Wnt pathway activation mechanism

In the absence of Wnts, (Fig. 1A), β-catenin in the cytoplasm is phosphorylated by glycogen synthase kinase 3β (GSK3β) and casein kinase 1 (CK1), both of which are parts of destruction complex that includes adenomatous polyposis coli (APC), axis inhibition protein (Axin) and β-transducin repeats containing protein (β-TrCP). In addition, phosphorylated β-catenin is ubiquitinated by β-TrCP and ultimately degraded by the proteasome [30–33]. When Wnt is present in the cytoplasm, (Fig. 1B), it will be lipidated by a special palmitoyl transferase-porcupine [34], further modified by Wntless in the Golgi and finally secreted by exocytosis [35,36]. Frizzled (FZD) receptors, the principal receptors for Wnts, consist of seven-transmembrane proteins and cysteine-rich domain (CRD) in the N-terminal [37,38]. Low-density lipoprotein receptor-related proteins (LRPs), the co-receptors of FZDs, are long single-pass transmembrane proteins. Wnt ligands bind to FZD or the CRD to induce the dimerization of FZD and LRP5/6 [4,39], as well as the phosphorylation of LRP5/6. Subsequently, phosphorylated LRP5/6 recruit Axin to membrane, and the destruction complex takes apart, which leads to the stabilization of β-catenin in cytoplasm [40]. After stabilization, β-catenin proteins translocate to the nucleus where they interact with the TCF/lymphoid enhancing factor (LEF) and sequentially activate downstream gene expression [41].

2.2. Relevant proteins and receptors in the Wnt/β-catenin pathway

Except for the above-mentioned proteins, other proteins, such as Wnt4, ring finger protein 43 (RNF43) [42], zinc and ring finger 3 [43], serine/threonine kinases [44], cellular homologue of myelocytomatosis viral oncogene (c-Myc), the cell cycle regulator D1 (cyclin D1) [45], surviving, Mitogen-activated protein kinase 1 as well as CK1e and traf2-and-nck-interacting kinase, have also been discovered to be closely associated with the Wnt signaling pathway, while different proteins appear to play different roles in biochemical signaling mechanisms. Moreover, a series of receptors are also involved in the Wnt/β-catenin pathway. Mitogen-activated protein kinase 1 [46], CK1e and traf2-and-nck-interacting kinase play pivotal roles in the activation of the Wnt/β-catenin pathway in β-catenin-dependent cancer cells. Inactivation of Wnt4 is vital for reproductive development of female mice [47]. Furthermore, Planutis *et al.* discovers that many transmembrane receptors, such as FZD1, FZD2, LRP4, roof plate-specific spondin (R-Spondin) and receptor-like tyrosine kinase/receptor tyrosine kinase-like orphan receptor 2 (ROR2), are also implicated in Wnt/β-catenin pathway [48]. However, all of corresponding signals output fully depend on the relative affinities between Wnt ligands and its receptors [49]. For instance, Wnt5a stimulates the stabilization of β-catenin target proteins by binding to FZD and LRP, while Wnt5a inhibits the β-catenin-dependent pathway via combining with ROR2. In addition, ROR2/planar cell polarity (PCP) autocrine signaling is activated when Wnt-8a binds to ROR2 [50].

3. Wnt/β-catenin pathway, diseases, natural small molecules

3.1. Cancers

3.1.1. Colon cancer

Colon cancer has high morbidity and mortality, representing the third leading cancer in men and the second leading cancer in women globally, with 1.2 million new cases and 600 000 deaths per year [51].

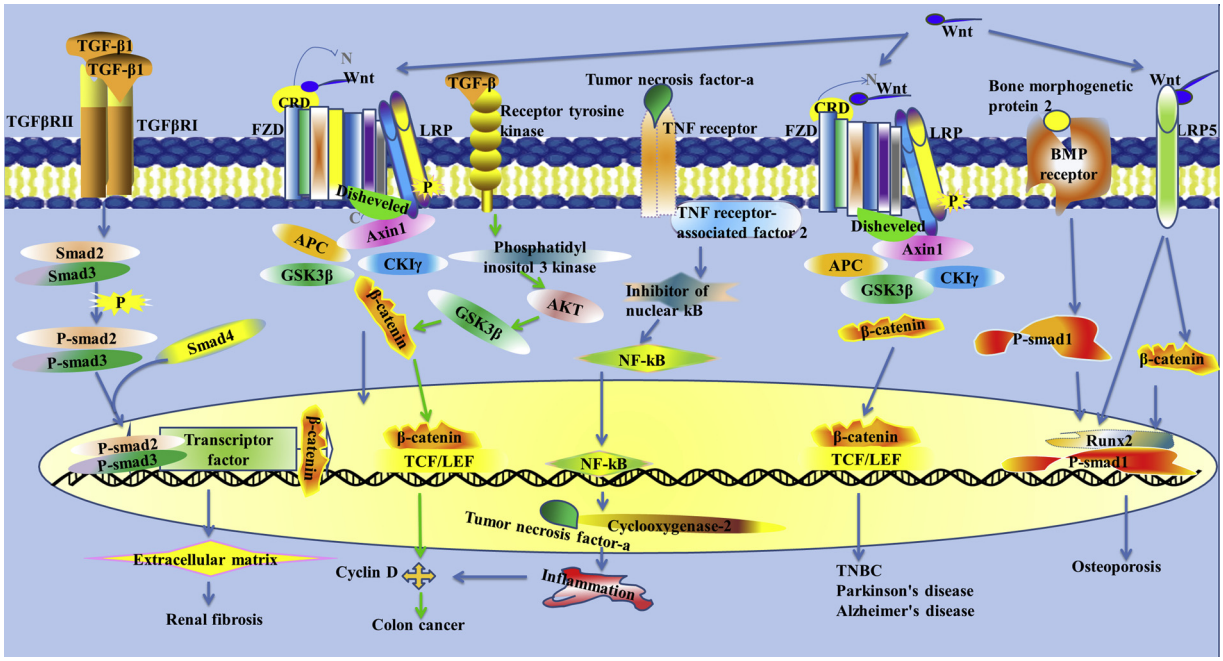

Fig. 2. Crosstalk between the Wnt/β-catenin pathway and TGF-β/Smad in renal fibrosis, phosphatidyl inositol 3 kinase/AKT and NF-κB in colon cancer, and bone morphogenetic protein 2/Smad in osteoporosis.

Table 1
The intervention effect of natural small molecules targeting Wnt/β-catenin pathway in diseases.

Diseases	Compound(s)	Therapeutic mechanisms	Reference(s)
Colon cancer	Ursolic acid Corosolic acid	Downregulating β-catenin and TCF-dependent gene expression	[59]
	Toosendanin	Inhibiting AKT/GSK3β/β-catenin pathway	[60]
	Triptonide	Inhibiting Wnt/β-catenin pathway	[61]
	Silibinin	Downregulating β-catenin and cyclin D 1 expression	[63]
	Quercetin	Downregulating c-Myc and cyclin D1 expression	[62]
	Apigenin	Inhibiting β-catenin/TCF/LEF pathway	[64]
	Berberine	Downregulating β-catenin expression	[65]
	Tetrandrine	Promoting β-catenin degradation and c-Myc downregulation	[66]
Breast cancer	Crocin	Downregulating FZD7 mRNA expression	[83]
	Triptolide	Inhibiting Wnt/β-catenin pathway	[86]
Renal disease	Poricoic acid (ZC, ZD, ZE, ZG and ZH)	Inhibiting Wnt/β-catenin pathway	[116,117]
	25-O-methylalisol F	Inhibiting Wnt/β-catenin pathway	[123]
Parkinson's disease	Curcumin	Inhibiting Wnt/β-catenin pathway	[128]
Osteoporosis	Harpagoside	Upregulating β-catenin, cyclin D1 and c-Myc expression and downregulating Dkk1 expression	[163]
	Dioscin	Inhibiting AKT/GSK3/β-catenin pathway	[140]
	Wedelolactone	Upregulating phosphorylated GSK3β and Runx2 expression and enhancing β-catenin nuclear translocation	[141]
	Kirenol	Upregulating β-catenin, LRP5, disheveled2, Runx2 and p-GSK3β expression	[142]
	Astragaloside I	Upregulating β-catenin and Runx2 expression	[143]
	Icariin	Upregulating Runx2 expression and enhancing β-catenin nuclear translocation	[144]
	Tricin	Upregulating Wnt3a expression and downregulating GSK3β expression	[146]
Rheumatoid arthritis	Resveratrol	Downregulating Wnt5a expression	[154]
	Epigallocat-echin-3-gallate	Inhibiting Wnt/β-catenin pathway	[155]
Hair growth	Ginsenoside F2	Upregulating β-catenin and LEF-1 expression and downregulating Dkk1 expression	[157]

A series of signaling pathways contribute to the pathogenesis of colon cancer, such as TGF-β/phosphatidyl inositol 3 kinase/protein kinase B (AKT), NF-κB and Wnt/β-catenin signaling cascade (Fig. 2), of which the Wnt/β-catenin pathway is dedicated contributor of colon cancer since the discovery of APC gene mutations [52]. Emerging studies have shown that the APC/β-catenin interaction, APC dysfunction [53] and RNF43 mutations [42,54] exacerbate aberrant Wnt signaling, leading to colon cancer, providing additionally evidence to previous studies. Moreover, R-Spondins and leucine-rich repeat containing G-protein coupled receptors 4–6 modules equally activate the Wnt/β-catenin pathway in various subtypes of colon cancer [43]. Reportedly, yes-associated protein and transcriptional co-activators with PDZ-binding motifs leave from destruction complex and accumulate in the nucleus, decreasing the survival of patients with colon cancer [55,56]. Furthermore, forkhead box protein O 3a, a transcriptional co-activator of β-catenin, interacts with β-catenin and simultaneously increases its concentration in the nucleus, which promotes local or distant tumour metastases and significantly attenuates the survival of colon cancer patients with stages 3 and 4 [57]. Interestingly, an Axin2 mutation has been recognized as a predisposing factor to colon cancer [58].

Ursolic acid and corosolic acid are natural pentacyclic triterpenoids from various plants, both of which have been clarificated as antagonists of the Wnt/β-catenin pathway in colon cancer cells. Intriguingly, a β-hydroxyl group at C-3 and carboxyl group at C-17 in ursolic acid were

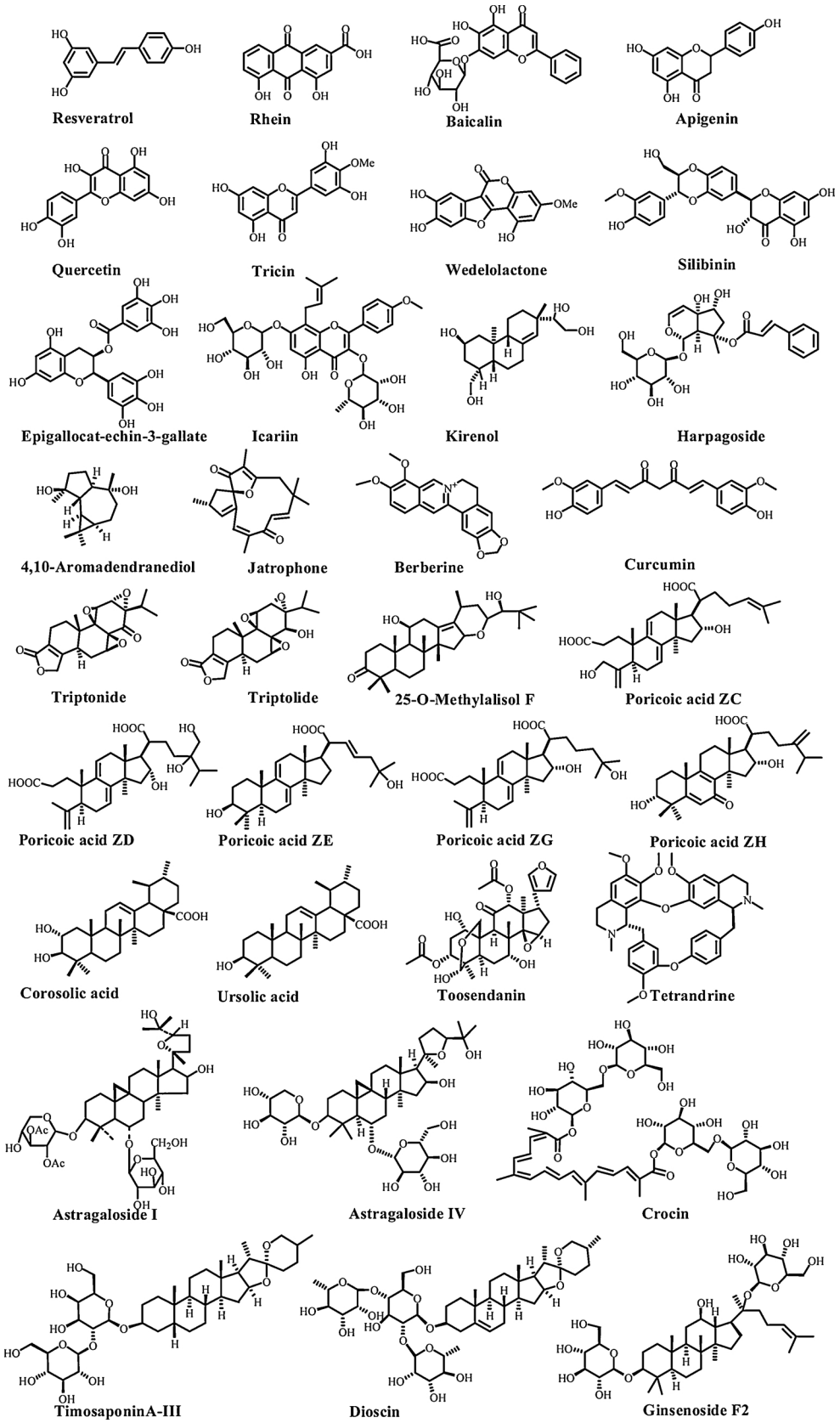

Fig. 3. Structures of natural small molecules from natural products.

previously proven to be cytotoxic to human promyelocytic leukaemia cells (HL-60), gastric cancer cells (BGC) and HeLa cells. Additionally, a carboxyl group at position C-17 and methyl group at position C-19 in ursolic acid were positively associated with β-catenin degradation and resistance to β-catenin/TCF interaction in ursolic acid-treated human colon cancer tissue 15 cells (HCT15) with APC mutation [59].

Terpenoids, toosendanin and triptonide, possess distinct anti-cancer mechanisms. Toosendanin extracted from the fruits or bark of *Melia toosendan* Sieb et Zucc subverts the AKT/GSK3β/β-catenin axis [60]. Triptonide in *Tripterygium wilfordii* Hook F. is identified as an inducer of apoptosis in human colon cancer cells (SW480 and RKO) and prostate cancer cell lines (PC3), which benefites from the suppression of triptonide in the Wnt pathway via targeting the C-terminal transcription domain of β-catenin or its nuclear co-factor instead of β-catenin translocation and β-catenin/TCF4 interaction [61]. Silibinin is a flavonolignan extracted from the seeds of milk thistle [62], and downregulated β-catenin as well as cyclin D 1 in polyps demonstrates the mechanism of silibinin against colon cancer in $APC^{min/+}$ mice [63]. Expression of c-Myc and cyclin D tends to be decreased in cancer stem cells and in HCT116 cells treated with quercetin, a flavonoid compound which is widely found in tea, berries, capers, onions, grapes and apples [62]. The flavonoid apigenin is widely found in fruits (orange, grapes and apples) and vegetables (parsley and onions). Recently, it is reported that apigenin could significantly inhibit proliferation, migration and invasion of colon cancer cells through suppressing activated β-catenin/TCF/LEF signaling cascades in human embryonic kidney 293T cells (HEK293 T) as well as SW480 cells. Moreover, apigenin also restrains β-catenin nuclear translocation in HCT15 cells and SW480 cells activated by LiCl in a concentration-dependent manner [64]. However, unlike ursolic acid, berberine is an isoquinoline alkaline from *Coptis chinensis* and demonstrates inhibitory effect on the expression, instead of the degradation of β-catenin in HCT116 cells [65]. Likewise, tetrandrine, an alkaloid bis-benzylisoquinoline isolated from the dried root of *Stephania tetrandra* S. Moore, confers resistance to proliferation and apoptosis in colon cancer via downregulating IGF binding protein 5 expression, which promotes β-catenin degradation and downregulates c-Myc expression in dimethylhydrazine- and dextran sodium sulphate-induced colorectal cancer LoVo cells [66].

Curcumin is a phenolic compound extracted from the rhizome of turmeric (*Curcuma longa*) that is usually used in Asia as an additive, spice and pigment [67–72]. Curcumin treatment suppressed the growth of colon cancer cells through retarding cell proliferation via inhibiting the Wnt/β-catenin pathway rather than by promoting apoptosis in mice [73]. Curcumin treatment also downregulated miR-130a expression, while miR-130a overexpression abolished the anti-tumour activity of curcumin [73].

3.1.2. Endometrial cancer

Endometrial cancer occurs in the endometrium in perimenopausal and postmenopausal women. Emerging evidence indicates that curcumin possesses chemopreventive properties against various cancers [74–76]. It has been reported that curcumin treatment inhibits proliferation and apoptosis of human endometrial carcinoma cells by downregulating expression of the androgen receptor and β-catenin in a concentration- and time-dependent manner [77]. Wnt3a partially nullifies the effects of curcumin on proliferation and apoptosis in human endometrial carcinoma cells, as well as the androgen receptor expression-downregulating effect of curcumin [77]. These findings confirm that curcumin might inhibit different cancers by repressing the Wnt/β-catenin pathway via miR-130a. Hence, the Wnt/β-catenin pathway may represent a new target of curcumin in cancer treatment.

3.1.3. Triple-negative breast cancer

Triple-negative breast cancer (TNBC) is the most metastatic subtype of breast cancer and cannot be overcome by standard therapy. Oestrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 are three major subtypes of breast cancer [78]. Wnt signaling is widely accepted as one of the most common sources for pro-proliferation signaling in TNBC cells, and the FZD7 protein may represent a novel target or biomarker for TNBC treatment [79]. XAV939 and clofazimine have been identified as Wnt inhibitors and promising anti-TNBC drugs, but neither of them have yet been used in advanced clinical trials [80,81]. Fortunately, tannins, isolated from *Syzygium guineense,* directly inactivates the stabilization and transcription of Wnt3a-induced β-catenin expression, which may be pursued for novel therapies [82]. As the most potent anti-cancer carotenoids in saffron, crocin exhibits a more potent anti-metastatic ability on TNBC through downregulating FZD7 mRNA expression and upregulating E-cadherin expression in the Wnt/β-catenin pathway [83]. In contrast to crocin, crocetin fails to impart its effects on the Wnt/β-catenin pathway [84]. Proanthocyanidins, isolated from Chinese bayberry leaf, attenuate expression of β-catenin, cyclin D1 as well as c-Myc, and block the G1 cell cycle as well as self-renewal ability in ovarian cancer stem cells (OVCAR-3 SP) [85]. Additionally, triptolide, isolated from *Tripterygium wilfordii* Hook F., has an inhibitory effect on myriad cancers, such as liver cancer, non-small cell lung carcinoma, osteosarcoma, pancreatic cancer as well as breast cancer, and has the capacity to remodel the activated Wnt/β-catenin pathway [86]. Taken together, natural products play an important role in various cancer interventions by regulating the Wnt/β-catenin pathway and Wnt/β-catenin signaling may represent a specific therapeutic target of natural small molecules against cancers.

3.2. Renal disease and fibrosis

Chronic kidney disease (CKD) is an epidemic that has increased by 73% from 1990 to 2013 and represents a primary cause of death worldwide. Renal fibrosis, characterized by tubulointerstitial fibrosis and glomerulosclerosis, is an inevitable outcome and final manifestation of all kinds of progressive CKD [87–91]. Renal fibrosis is closely associated with mounting mediators and signaling pathways, such as oxidative stress, inflammation, microRNAs, transforming growth factor β1 (TGF-β1)/Smad and Wnt/β-catenin (Fig. 2), as well as the dysregulated uremic toxins, amino acids and lipid metabolism [92–100]. In recent decades, natural small molecules have gradually become an important therapeutic strategy for the prevention and treatment of renal fibrosis worldwide [22,101,102]. Emerging studies suggest that small molecular compounds isolated from natural products exert good therapeutic effects on renal disease and fibrosis [103–106]. A number of traditional Chinese medicines, such as *Poria cocos* (PC)*, Alismatis rhizoma* and *Polyporus umbellatus*, promote urination and eliminate oedema, both of which are associated with the retardation of renal disease and fibrosis.

PC grows around the roots of pine trees in Asia and North America [107]. PC and its surface layer have diuretic effects [108,109], antihyperlipidemic activity [110,111] and CKD treatment potential [112–115]. Our study reported that poricoic acid ZG and poricoic acid ZH, isolated from the surface layer of PC, significantly ameliorated the upregulated expression of Wnt1 and β-catenin, as well as its target gene expression, including Snail1, Twist, matrix metalloproteinase 7, plasminogen activator inhibitor 1 and fibroblast specific protein 1 in TGF-β1-induced human kidney proximal epithelial cells (HK-2). Interestingly, poricoic acid ZG and poricoic acid ZH also selectively suppressed Smad3 phosphorylation through alleviating the interactions of smad anchor for receptor activation with TGF-β receptor I and Smad3 in the TGF-β/Smad pathway. Structure-function analysis indicated that the antifibrotic effect was associated with the first six-membered ring structure and the number of carboxyl groups in tetracyclic triterpenoid compounds [116]. In addition, we also obtained three new triterpenoids, including poricoic acid ZC, poricoic acid ZD and poricoic acid ZE, and discovered that they could significantly alleviate extracellular matrix production by suppressing the Wnt/β-catenin pathway and specific Smad3 phosphorylation via blocking the interaction of TGF-β receptor I with Smad3 signaling in TGF-β1 or angiotensin II-induced HK-2 cells and unilateral ureteral obstructive mice [117]. Structure-activity analysis suggested that secolanostane tetracyclic triterpenoid compounds, poricoic acid ZC and poricoic acid ZD, showed a stronger inhibitory effect than lanostane tetracyclic triterpenoid compound

poricoic acid ZE, indicating that compounds with a secolanostance skeleton exhibit stronger bioactivity than those with a lanostance skeleton.

*Alismatis rhizom*e, the dried stem tuber of *Alisma orientale* (Sam.) Juzep., exerts powerful diuretic, anti-hyperlipidemic effects, which may be intimately associated with the anti-fibrotic effect. [118–122]. Triterpenoid compounds are the primary active components in *Alismatis rhizome* [118,123]. 25-O-methylalisol F is a new tetracyclic triterpenoid compound isolated from the *Alismatis rhizome*. Our latest study find that 25-O-methylalisol F inhibits upregulated expression of Wnt1 as well as β-catenin and its target gene expression, including Snail1, Twist, matrix metalloproteinase-7, plasminogen activator inhibitor 1 and fibroblast specific protein 1, in both TGF-β1-induced HK-2 cells and normal rat kidney interstitial fibroblast cells (NRK-49 F). In addition, 25-O-methylalisol F inhibits Smad3 phosphorylation and maintains Smad7 expression in the TGF-β/Smad-dependent pathway, exerting a strong inhibitory effect on crosstalk between Wnt/β-catenin and TGF-β/Smad pathways in the extracellular matrix [123]. Collectively, the Wnt/β-catenin pathway may be a specific therapeutic target of natural small molecules against renal fibrosis.

3.3. Neurodegenerative diseases

Parkinson's disease is the second most common neurodegenerative disease, affecting approximately 1% of the population aged 65 or older worldwide [124]. Emerging management of Parkinson's disease has primarily focused on inhibitor medications, such as levodopa, dopamine agonists, monoamine oxidase type B and catechol O-methyltransferase inhibitors. In addition, surgery, rehabilitation and palliative care are used for Parkinson's disease treatment as well [125]. The causes of Parkinson's disease are attributed to age, low serum urate concentrations, smoking, α-synuclein mutations, leucine-rich repeat kinase 2, phosphatase, tension homolog-induced putative kinase 1, parkin 7, vacuolar protein sorting 35, receptor-mediated endocytosis 8 as well as coiled-coil-helix-coiled-coiled-helix domain containing 2 [124] and eukaryotic translation initiation factor 4-γ [126]. In addition, leucine-rich repeat kinase 2 mutations also exacerbate disease progression by activating the Wnt/β-catenin pathway in adult mice and cultured fibroblasts [127]. It has been reported that curcumin isolated from the rhizome of turmeric (*Curcuma longa*) exhibits neuro-protective effects and attenuates bisphenol A (BPA)-induced neurotoxicity through inhibiting activated Wnt/β-catenin signaling, verified by the use of Wnt specific activators, such as LiCl, GSK3β siRNA and inhibitor dickkopf (Dkk) 1. Curcumin treatment significantly reverses BPA-mediated increased β-catenin phosphorylation, downregulated GSK3β expression and β-catenin nuclear translocation in neural stem cells [128]. Meanwhile, neurogenesis as well as learning and memory in BPA-treated rats were improved in response to curcumin [128]. These data indicate that curcumin exhibits neuroprotection against BPA-mediated impaired neurogenesis through depressing activated Wnt/β-catenin signaling.

Neurogenesis, the process of generating new neurons, is reduced in several neurodegenerative disorders including Alzheimer's disease. It has been reported that curcumin nanoparticles improve neuronal differentiation via decreasing the expression of GSK3β, with enhanced β-catenin nuclear translocation and promoter activity of the TCF/LEF and cyclin D1 [129]. Treatment with curcumin nanoparticles further reverses learning and memory impairments by inducing neurogenesis in an amyloid β-induced rat model of Alzheimer's disease [129]. Moreover, molecular docking studies indicates that curcumin interacts with Wif-1, Dkk, and GSK3β. Collectively, these findings demonstrate that curcumin treatment induces adult neurogenesis via activating the Wnt/β-catenin pathway and improving the brain's self-repair mechanisms, which might represent a therapeutic intervention for neurodegenerative diseases, such as Parkinson's and Alzheimer's. Therefore, the Wnt/β-catenin pathway may be exploited for a specific therapeutic target of natural small molecules in the treatment of neurodegenerative disease.

3.4. Bone disorders

The balance between osteoblasts and osteoclasts plays significant roles in bone formation and maintenance, the loss of which results in bone disorders, including osteoporosis [130]. As an age-dependent metabolic bone disorder, osteoporosis has two main characteristics, low bone mass and micro-architectural deterioration of bone tissue [131]. Unfortunately, current therapeutic strategies for osteoporosis are mainly focused on physical exercise and medications, such as bisphosphonates, teriparatide, strontium ranelate and denosumab [132]. Except for the pathogenic factors, the occurrence of osteoporosis is attributed to both non-modifiable risk factors, such as gender, race, heredity, age, and modifiable risk factors, such as medical disorders, hypogonadal states, endocrine disorders, vitamin D deficiency and long-term intake of proton pump inhibitors [133,134]. Emerging evidence suggests that bone morphogenetic protein 2/Smad and Wnt/β-catenin pathways (Fig. 2) are associated with osteoporosis [135–137]. Enhanced β-catenin phosphorylation and GSK3β in senile osteoporosis indicate that the Wnt/β-catenin pathway is a possible therapeutic target in the treatment of osteoporosis [138].

Iridoid glycoside harpagoside, a major bioactive component of the radix of *Harpagophytum procumbens* var. *sublobatum* (Engl.) Stapf (Pedaliaceae), exhibits analgesic, anti-inflammatory, anti-phlogistic and anti-osteoporotic effects. Harpagoside treatment induces osteoblast differentiation via upregulating the expression of β-catenin, cyclin D1 as well as c-Myc and downregulating Dkk1 expression [139]. *in vitro* and *in vivo* experiments demonstrate that the AKT/GSK3/β-catenin axis in osteosarcoma is probably inhibited by steroidal saponin dioscin, a major compound of Liuwei Dihuang decoction and Di'ao Xinxue kang [140].

As a derivative of coumarin, wedelolactone, isolated from *Ecliptae herba* with the capability of nourishing bones, enhances osteoblastogenesis in mouse bone marrow mesenchymal stem cells through enhancing β-catenin nuclear translocation and increasing levels of phosphorylated GSK3β protein as well as runt-related transcription factor 2 (Runx2) protein in the Wnt/GSK3β/β-catenin pathway [141]. Additionally, it is demonstrated that the terpenoids kirenol, astragaloside I and flavone icariin have similar effects on the Wnt/β-catenin pathway and osteoblastic differentiation. Diterpenoid kirenol isolated from *Herba Siegesbeckiae* promotes osteoblast differentiation in mouse osteoid cell lines (MC3T3-E1) and accelerates the upregulation of LRP5, disheveled2, Runx2, p-GSK3β as well as β-catenin in the Wnt/β-catenin pathway, contributing to osteoblast differentiation [142]. Upregulated expression of β-catenin and Runx2 has also been shown in MC3T3-E1 cells treated with Astragaloside I isolated from *Astragalus membranaceus* [143], which possesses osteogenic properties and exhibits partially similar effects as icariin on the Wnt/β-catenin pathway with respect to osteoblastic differentiation. Icariin is extracted from *Epimedium brevicornum* Maxim, which promotes proliferation, differentiation and mineralization of osteoblasts in MC3T3-E1 cells via enhancing nuclear translocation of β-catenin and upregulating the mRNA and protein expression of Runx2 [144]. Except for increased β-catenin and Runx2, the expression of cyclin D1 and alkaline phosphatase is elevated in icariin-treated osteoblastic cells from rat mandible [145]. In addition to icariin, flavone tricin, rich in rice bran or other grass species, enhances osteoblastogenesis through upregulating Wnt3a expression while downregulating GSK3β expression in human adult mesenchymal stem cells [146]. Taken together, the Wnt/β-catenin pathway may be an attractive therapeutic target of natural small molecules for the treatment of bone disorders.

3.5. Other diseases

Rheumatoid arthritis is a chronic inflammatory illness that displays painful swelling or inflammation of the synovial lining in the joints and cartilage, as well as ultimate bone damage [147]. Mutations in CD28

and CD40 or genetic variants of LRP5 in the Wnt/β-catenin pathway are risk factors for bone damage in patients with rheumatoid arthritis [148]. Both upregulated expression of Wnt5a or β-catenin play prominent roles in the Wnt/β-catenin pathway in cultured fibroblast-like synoviocytes from rheumatoid arthritis patients [149]. Fortunately, newly emerging anti-sclerostin therapies (romosozumab and blosozumab) and several natural small molecules have shown a beneficial effect on the treatment of rheumatoid arthritis through targeting the Wnt/β-catenin pathway. Resveratrol, a natural polyphenolic compound isolated from plants, has various physiological effects, including anticancer and anti-cardiovascular, and is expected to become a promising natural product for clinical use, despite most related studies being performed in animal models [150–153]. In collagen-induced arthritis mice, levels of Wnt5a protein are decreased and the Wnt/β-catenin pathway is suppressed by resveratrol [154]. Similar to resveratrol, curcumin and epigallocat-echin-3-gallate isolated from green tea suppress arthritis and have an inhibitory effect on the Wnt/β-catenin pathway [155,156]. Intriguingly, as a metabolite of ginsenoside-Rb1, ginsenoside F2 positively regulates the anagen phase and hair growth through upregulating expression of β-catenin as well as LEF-1 and downregulating expression of Dkk1 [157].

In addition, emerging studies have demonstrated that mutations in Wnt/β-catenin signals are closely linked to multiple diseases, such as synovial sarcoma, type II diabetes and myocardial fibrosis. Aberrant Wnt signaling and added β-catenin stabilization have been termed secondary changes in synovial sarcoma, but effective therapy for the treatment of synovial sarcoma remains to be determined [158], encouraging further research to block synovial sarcoma tumour formation by inhibiting the Wnt/β-catenin pathway. Mutations in Wnt5b and transcription factor 7-like 2 are observed in type II diabetes [159]. Downregulated Wnt5a, FZD-related proteins and Dkk1 are discovered in mutant pancreatic mesenchyme [160] and Wnt/β-catenin pathway is activated in intervertebral disc cells [161], which is highly consistant with previous findings. Additionally, overexpression of Wnt1 and Wnt5a or the inhibitory activities of Wnt-C59 on Wnts are all evidence of the critical role of the Wnt/β-catenin pathway in myocardial fibrosis progression and myofibroblast formation [162]. Unfortunately, thus far, no effective natural small molecules have been applied to treat these diseases that act through the Wnt/β-catenin pathway. Thereby, these studies might provide a new avenue for natural small molecules targeting the Wnt/β-catenin pathway in various diseases.

4. Concluding remarks

In summary, this systemic review examined the intervention of natural small molecules on Wnt/β-catenin pathway with respect to initiation and progression of cancers, renal diseases, neurodegenerative diseases and bone disorders. Through elaborating on the mechanisms of Wnt/β-catenin pathway using *in vitro* and *in vivo* experiments, further insights into these mechanisms enable in-depth understanding of the pathophysiology of those diseases and facilitate discovery of targeted therapeutic agents.

After a pooled analysis of clinical and non-clinical natural products, chemotherapeutic drugs and biological agents against the Wnt/β-catenin pathway, we learned that intracellular porcupine, extracellular Wnt ligands as well as their receptors, and β-catenin-dependent proteins, have become major targets of antagonists. Clinical trials have shown that porcupine is a target of a novel inhibitor, ETC-159, with poor oral bioavailability. Wnt3a is regarded as a target of microRNA-15a-5p and microRNA-195 in colon cancer. LRP6 and FZD7/FZD8-Fc are concurrently thought to be targets of sclerostin and nigericin. Moreover, β-catenin expression is regulated by natural berberine and sulphoraphane, while β-catenin-dependent proteins are targeted by natural compounds, such as epigallocat-echin-3-gallate, triptonide, ursolic acid and toosendanin. In addition, interactions between β-catenin and APC, TCF or CBP are inhibited by cercosporin, baicalein and ICG-001, respectively. Unfortunately, with further research on antagonists, a series of side effects have been discovered, which severely restrict their use. For example, R-Spondins inhibitor causes differentiation of colon tumour cells and loss of stem cell function. Long-term users of the GSK3 inhibitor lithium are diagnosed with a significantly higher incidence of renal cancers. As such, it is imperative to seek safe and effective targeted therapeutics to resolve the prominent problems that continue to puzzle the biomedical community.

With the in-depth understanding of the mechanisms of aberrant Wnt/β-catenin pathway in diseases, seeking targeted agents against mutations in Wnt/β-catenin signals have drawn increasing attentions. Of note, rich natural resources, together with advanced biotechnology, have also offered increasing possibilities for the development of novel drugs and targeted agents. Excluding the natural small molecules mentioned above (Table 1), natural rhein and baicalin, along with natural terpenoids (timosaponin AIII, astragaloside IV, jatrophone and 4,10-aromadendranediol), have also been investigated and confirmed as promising compounds against the mutant Wnt/β-catenin pathway (Fig. 3), which greatly inspires us to identify more targeted compounds from nature. Notably, the generation of targeted natural small molecules not only improves defects of existing therapeutic agents but also provides opportunities for the treatment of diseases, such as the type II diabetes, synovial sarcoma and myocardial fibrosis.

Conflict of interest

No potential conflict of interests exists.

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