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Review Article

Ginseng-derived compounds as potential anticancer agents targeting cancer stem cells

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ABSTRACT

Cancer stem cells (CSCs) are a rare subpopulation of cancer cells that exhibit stem cell-like characteristics, including self-renewal and differentiation in a multi-stage lineage state via symmetric or asymmetric division, causing tumor initiation, heterogeneity, progression, and recurrence and posing a major challenge to current anticancer therapy. Despite the importance of CSCs in carcinogenesis and cancer progression, currently available anticancer therapeutics have limitations for eradicating CSCs. Moreover, the efficacy and therapeutic windows of currently available anti-CSC agents are limited, suggesting the necessity to optimize and develop a novel anticancer agent targeting CSCs. Ginseng has been traditionally used for enhancing immunity and relieving fatigue. As ginseng's long history of use has demonstrated its safety, it has gained attention for its potential pharmacological properties, including anticancer effects. Several studies have identified the bioactive principles of ginseng, such as ginseng saponin (ginsenosides) and non-saponin compounds (e.g., polysaccharides, polyacetylenes, and phenolic compounds), and their pharmacological activities, including antioxidant, anticancer, antidiabetic, antifatigue, and neuroprotective effects. Notably, recent reports have shown the potential of ginseng-derived compounds as anti-CSC agents. This review investigates the biology of CSCs and efforts to utilize ginseng-derived components for cancer treatment targeting CSCs, highlighting their role in overcoming current therapeutic limitations.

1. Introduction

Cancer is the leading cause of death worldwide, and the burden associated with cancer is expected to increase progressively [1,2]. Despite the extensive research to develop anticancer therapies and the great advances in understanding cancer biology, cancer remains difficult to cure, primarily due to metastasis and recurrence. Cancer is a collection of heterogeneous cell populations, referred to as intratumor heterogeneity [3], which poses the greatest challenges to anticancer therapy. The intratumor heterogeneity determines the therapeutic outcome, as even each cancer cells of the same origin exhibit subtle or obvious differences, emphasizing the need to comprehend the underlying biology for effective anticancer treatments. The cancer stem cells, distinguished by their ability for self-renewal and multi-lineage differentiation, drive tumor initiation and heterogeneity as well [4,5]. The hierarchy of cancer cells is not rigid, but rather flexible which is represented by the plasticity of CSCs, making this to be a key factor in understanding the intratumoral heterogeneity [5,6]. Although the mechanism by which CSCs contribute to cellular heterogeneity within tumors still needs to be investigated, clinical evidence of the existence of CSCs in many types of cancer [7] drives anticancer research to discover therapeutics targeting CSCs in order to eradicate cancer completely.

Utilizing natural products and structurally similar compounds in anticancer therapy offers benefits, including low toxicity and a valuable model for lead compounds, leading to substantial contributions to anticancer therapeutics through endeavors to identify bioactive molecules from natural sources [16,17]. Recent research has investigated the pharmacological potential of ginseng, which has been used for centuries in East Asian traditional medicine for the purpose of strengthening immunity and relieving fatigue. Among the 8 to 13 species in the genus *Panax*, three species are widely known as major sources of traditional medicine: *P. ginseng* (Asian or Chinese ginseng), *P. quinquefolius* (American ginseng), and *P. notoginseng*. The traditional use of ginseng for medical purposes is restricted to specific regions (mostly East Asian

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countries), and its mechanism of action remains to be investigated. With the aid of accumulating research on the bioactive compounds of ginseng, its potential use has been extended to anticancer therapies. In this review, we will discuss current efforts to identify the use of ginseng-derived components in anticancer therapies, especially those targeting CSCs, to overcome the current therapeutic limitations.

2. Biology of cancer stem cells

2.1. The definition of cancer stem cells

CSCs are characterized by a sluggish proliferative rate, resistance to conventional anticancer therapy, and a flexible differentiation capacity that enables them to easily adapt to severe survival conditions; all of these characteristics are intimately linked to cancers that are difficult to treat [18]. A higher proportion of undifferentiated cancer cells in the residual mass after chemotherapy is associated with a poor prognosis, demonstrating the clinical presence of CSCs [7]. To prove the presence of CSCs in experimental conditions, identification of CSC-associated markers, techniques for monitoring CSCs, and in vivo models for determining their tumorigenic function have become essential for functional studies of CSCs. The expression of cell surface markers has been most extensively studied to distinguish CSCs from non-CSCs, and these include $CD34^{+}CD38^{-}$ (leukemia) [19], $CD44^{+}CD24^{-/low}$ (breast cancer) [20], $CD133^{+}$ (brain tumor and lung cancer) [21–23], $CD44^{+}\alpha_2\beta_1^{hi}CD133^{+}$ (prostate cancer) [24], and $CD44^{+}CD117^{+}$ (ovarian cancer) [25]. Additionally, cells exhibiting elevated aldehyde dehydrogenase (ALDH) activity have been demonstrated to possess tumorigenic potential, establishing ALDH activity as a distinguishing factor between CSCs and non-CSCs [26–28]. Notably, although CSCs are essential for the development of cancer, the characteristics of CSCs defined by various approaches do not always overlap, indicating that the CSC population is also heterogeneous [29].

2.2. Role of CSCs in cancer progression and development

Cancer is a multistep process that begins with a single cell proliferating abnormally due to genetic or epigenetic alterations, followed by the selection of a population of cells with higher proliferative potential, resulting in the formation of a primary mass tumor and progressing into metastasis [30]. Since CSCs can generate multiple types of tumor cells and are intimately engaged in the entire process of cancer development and progression (Fig. 1), it is crucial to comprehend the alterations that occur in CSCs during the progression of cancer.

2.2.1. CSCs in tumor initiation

The defining characteristic of a CSC is the capacity to generate other cell types within the tumor and initiate cancer in vivo; consequently, the presence of a CSC population is required for tumor initiation [18]. The presence of CSC was first identified in human acute myeloid leukemia (AML) by the observation that $CD34^{+}CD38^{-}$ cells isolated from AML cells developed tumors in severe combined immune deficient (SCID) mice while the $CD34^{+}CD38^{+}$ or $CD38^{-}$ cells did not [19]. Based on the stem cell markers of their normal counterparts, this discovery prompted efforts to identify CSC in other solid malignancies. In cells isolated from breast cancer patients, only $CD44^{+}CD24^{-/low}$ population of cells generated tumors in non-obese diabetic (NOD)/SCID mice, even in only hundred cells-implanted mice [20]. In brain tumors, $CD133^{+}$ cells held a marked ability to self-renew, possess stem cell activity, and form tumors in NOD/SCID mice [21,22]. Once the tumor initiated, CSCs support the growth of the primary tumor through recruitment and modulation of tumor microenvironment components, such as activation of

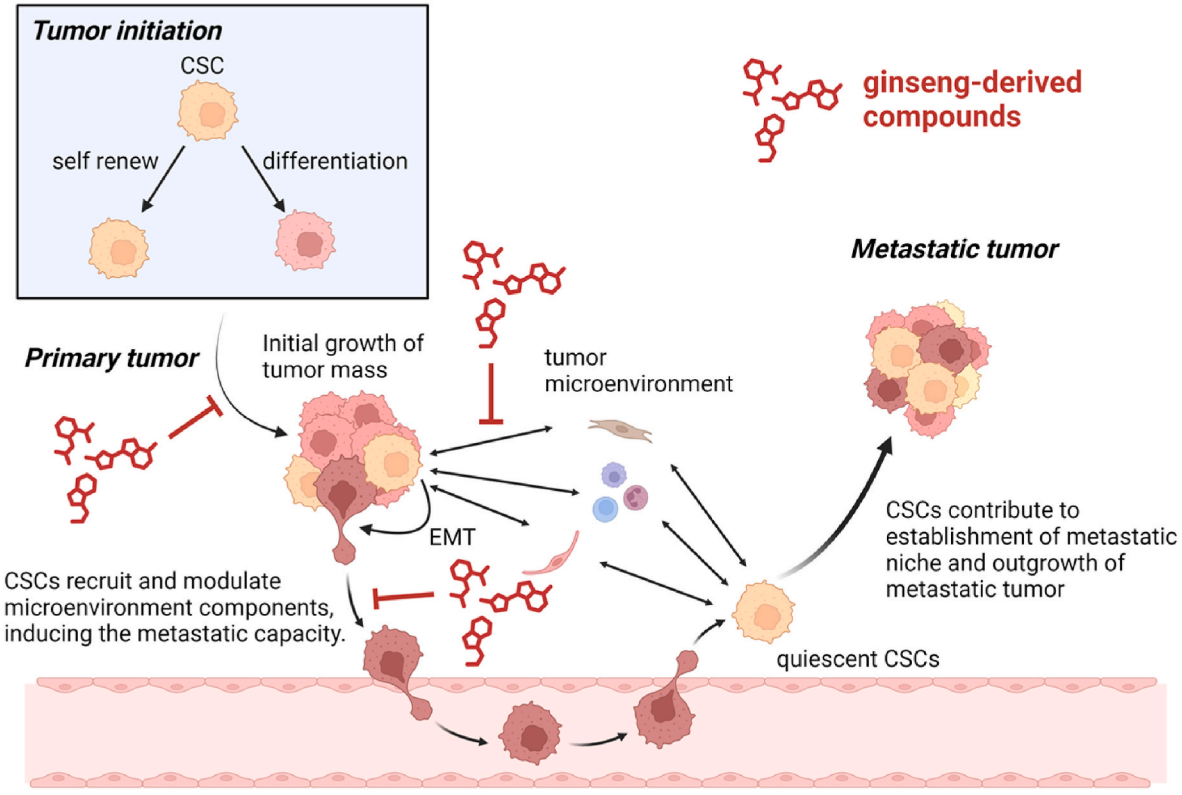

Fig. 1. CSCs in the initiation and progression of cancer and their inhibition by ginseng-derived compounds. The capacity of the CSC to generate multiple types of cancer cells within the tumor is essential for the development of primary tumors. CSCs interact with tumor surveillance microenvironment components to support the expansion of the tumor as the primary tumor growth mechanism. Cells with stemness properties transition to invasiveness, persist, and translocate to metastatic sites while remaining quiescent. During colonization, CSCs support the growth of metastatic tumors by evading immune surveillance and promoting the proliferation of quiescent CSCs.

angiogenesis, evasion of antitumor immunity, and regulation of the extracellular matrix [31]. Invasion of the neighboring tissue, the initial phase of the metastatic cascade, is also dependent on these functions.

2.2.2. CSCs in metastasis

The regulatory mechanism of cancer metastasis is largely unknown, despite the fact that cancer metastasis is the primary cause of cancer-related mortality [32]. The metastasis cascade is simplified into two steps: 1) physical translocation from the primary site to the site of dissemination, and then 2) colonization [32]. Considering that colonization at a metastatic site is analogous to the beginning of a tumor in a host, it appears that CSCs is the major population that drives metastasis [33]. In addition, it has been demonstrated that CSCs share characteristics with highly metastatic cancer cells, such as being highly invasive and resistant to apoptotic signals [34]. Additionally, epithelial-to-mesenchymal transition (EMT) suggests a link between CSCs and metastasis. It has been well known that CSC properties are regulated by master EMT transcription factors, such as Snail and Twist1; This connection between EMT and CSCs suggests that CSC hierarchies are flexible [5]. All of these findings support the hypothesis that CSCs are essential for metastasis, reiterating the therapeutic importance of CSC research.

2.3. Small molecule inhibitors targeting CSCs

CSCs are typically more resistant to chemotherapies, which is closely related to their molecular characteristics, such as high expression of ATP-binding cassette (ABC) transporters, which increases drug efflux; high ALDH activity, which neutralizes the effect of chemotherapeutic drugs; and upregulation of antiapoptotic proteins (Bcl-2 and Bcl-xL) [35]. Therefore, targeting signaling pathways that are dysregulated in CSCs is more advantageous than conventional chemotherapies for incapacitating CSCs. Wnt/β-catenin, Notch and Hedgehog (Hh) pathways have been extensively studied as a CSC-supporting signaling pathways. Despite extensive research on CSC-related signaling pathways and the development of molecularly targeted therapeutics against these pathways, it is unknown whether these reagents target CSCs in clinical studies. This is due to the technical limitation that it is challenging to examine CSCs in clinical trials, or the possibility that clinical trials are not lengthy enough to observe therapeutic efficacy in CSCs. Nonetheless, the results of these therapeutics have been quite encouraging.

Cyclopamine, a steroidal alkaloid isolated from *Veratrum californicum*, was discovered as a Hh pathway inhibitor (via binding to SMO) and it reversed the aberrant growth caused by oncogenic mutations in *PTCH* and *SMO*, indicating the therapeutic potential of Hh pathway-targeting medications in the treatment of cancer [36]. Vismodelgib (GDC-0449) and sonidegib (LDE225) are FDA-approved Hh pathway inhibitor [37,38], but whether these inhibitors target CSCs has not been demonstrated yet.

Multiple classes of Notch pathway inhibitors, such as γ-secretase inhibitors, ADAM inhibitors, monoclonal antibodies against the DLL, and γ-secretase modulators, have been developed, with γ-secretase inhibitors being the most extensively investigated category [39]. In a preclinical investigation, the γ-secretase inhibitor MK-0752 reduced breast CSCs, and in a clinical study, it demonstrated the feasibility of combination therapy with chemotherapy [40]. Demcizumab (OMP-21M18) is a humanized anti-DLL4 antibody that significantly inhibited colon cancer tumor growth and CSC-related phenotypes in preclinical studies [41,42]. In addition, numerous natural products, including cinobufagin, diallyl trisulfide, artemisinin, and baicalein, have been reported to modulate the Notch signaling pathway and exert anticancer effects [39]. Due to the extensive spectrum of the Notch signaling pathway's function, the narrow therapeutic window limits the clinical utility of Notch-targeting drugs. While preclinical studies support the efficacy of these therapeutics, the results of clinical studies when used as monotherapy are disappointing [43]. Numerous clinical trials of Notch-targeting drugs are ongoing, particularly in terms of combination therapy; therefore, toxicity studies in these contexts would be a prerequisite for the clinical application of these drugs.

The Wnt signaling pathway poses a challenge as a target because the majority of its components are involved in other cellular processes and its regulation is highly dependent on protein-protein interactions. The Wnt signaling pathway is targeted by porcupine inhibitors, which inhibit the secretion of Wnt ligands, Wnt antagonists, LRP5/6 inhibitors, and β-catenin activity inhibitors. OMP-54F28 (decoy receptor to Wnt ligands) and PRI-724 (β-catenin inhibitor) showed clinical activity in desmoid tumor [44] and pancreatic cancer [45], respectively. Wnt pathway-targeting medications, like those that target the Hh or Notch signaling pathways, have a very narrow therapeutic window [46]. Consequently, development strategies for cancer-specific targeting can improve their effectiveness. The liposome encapsulation of CGX1321 (a porcupine inhibitor) enabled cancer-specific disruption of the Wnt pathway while sparing other cells from cytotoxicity, along with a CSC-targeting effect [47].

2.4. CSC-targeting immunotherapies

As previously mentioned, the primary disadvantage of molecular targeted therapies against the Hh, Notch, and Wnt signaling pathways is their limited therapeutic window, because of the signaling pathways' involvement in numerous biological processes [43,46]. Consequently, it is crucial to identify the main mechanisms that support CSCs in various types of cancer and to classify the specific CSC population that can benefit from a particular therapy. Immunotherapy that targets CSCs independently of signaling pathways would be an alternative option from a safety standpoint.

Currently, there are no CSC-specific immunotherapies available for clinical use; however, in preclinical studies, the application of CSC-specific markers to immunotherapies has proven to be quite promising. Vora et al. devised and evaluated the efficacy of three immunotherapeutic regimens targeting CD133 in glioblastoma (GBM) models [48]. All three modalities (monoclonal antibody, dual-antigen T cell engager, and CAR-T cells) inhibited tumor growth in humanized mouse models, with CAR-T cells having the most potent effect with minimal toxicity [48]. As a result of the fact that many characterized CSC markers are actually derived from expression in normal stem cells, it is essential to identify novel markers exhibiting exclusive expression in the CSC population as immunotherapy targets. An HLA ligandome analysis identified ASB4 as a tumor-specific antigen with enriched expression in colorectal CSC populations and the ability to induce the cytotoxic T-cell response [49]. Immunotherapy is a potent therapy for patients with treatment-resistant primary cancer because it is more likely to exert a protracted efficacy and to identify a therapy-favorable patient population than other anticancer therapies.

3. Possibility of ginseng-derived compounds serving as CSC-targeting agents

The prevalence of widely used chemotherapeutic agents derived from natural products underscores the significant role of natural products in the development of anticancer therapies. These chemotherapeutic agents include paclitaxel (isolated from *Taxus brevifolia*), vinblastine (isolated from *Catharanthus roseus*), etoposide (a semisynthetic derivative of podophyllotoxin isolated from *Podophyllum peltatum*), doxorubicin (isolated from *Streptomyces peucetius* bacterium), and cytarabine (a semisynthetic derivative of C-nucleoside-derived compounds isolated from *Cryptotheca crypta*), and they have been routinely used in cancer treatment for several decades [50–53]. The potential of natural products as a drug candidate has been well recognized, and growing attempts to find natural products with anti-cancer activity has been made. Due to its diverse pharmacological activities, ginseng has been a useful source for drug discovery in the cancer field.

The anticancer effect of ginseng has been reported in several studies, as thoroughly reviewed by Ahuja et al. [54–56]. Based on these supporting studies, researchers have focused on identifying the molecular mechanisms of anticancer effects of ginseng-derived compounds to translate experimental findings into clinical applications.

3.1. Classification of ginseng-derived compounds

Physiologically active compounds derived from ginseng includes ginsenosides, polysaccharides, peptides, polyacetylenes, phenolic compounds, terpenes, and fatty acids [57,58]. Among these, ginsenosides, also known as ginseng saponins, stand out as the most extensively researched bioactive compounds due to their distinctive presence in *Panax ginseng*. Ginsenosides are further categorized according to the structure of their genin (aglycon): the four-ring dammarane family and the oleanane family, with protopanaxadiols (including Rb1, Rb2, Rg3, Rh2 and Rh3) and protopanaxatriols (including Rg1,Rg2, and Rh1) being the main functional categories within the dammarane family [59].

3.2. Molecular mechanism of targeting CSCs by ginseng-derived compounds

Since many studies have shown promising anticancer effect of ginseng-derived compounds, the needs for identifying the mechanism of action have also been growing in this field. Due to the fact that ginseng contains a variety of bioactive compounds, it exerts anticancer effects in various aspects of cancer progression, including proliferation, invasiveness, angiogenesis and emergence of drug resistance [60–64]. Especially, studies have demonstrated that compounds derived from ginseng sensitize cancer cells to anticancer therapy, implying that ginseng also inhibits tumor heterogeneity [65,66]. Rg3 exerted a synergistic effect on cisplatin-resistant bladder cancer cell lines, but had no effect on cisplatin-sensitive cell lines, demonstrating the effects of ginseng-derived compounds on therapy-resistant cancer cells [66]. This highlights the potential of ginseng-derived compounds as a CSC-targeting therapy which will benefit targeting aggressive cancer. Indeed, it has been documented that ginseng-derived compounds modulate CSC-related signaling pathways and reduce the CSC population, enabling better understanding of molecular mechanism of CSC-targeting effect of ginseng-derived compounds (see Table 1). In this review, we will discuss the key major signaling pathways that regulate CSCs and how ginseng-derived compounds affect each pathways. We will first discuss studies on ginsenosides (also known as ginseng saponin), a major ingredient of ginseng, then cover the studies on anticancer effects of non-saponin components.

Table 1
CSC-targeting activity of ginseng-derived compounds with known mechanisms.

Classification	Compound	Cancer types	Mechanism of action	References
Ginsenosides	**Rb1**	Ovarian cancer	Inhibition of the Wnt/β-catenin pathway	[8]
	Rg3	Lung cancer	Inhibition of the hypoxia-induced NF-κB signaling pathway	[9]
	Rg3	Breast cancer	Inhibition of the PI3K pathway	[10]
	Rg3	Breast cancer	Inhibition of the MDSC-induced Notch pathway	[11]
	Rg3, Rh1	Glioblastoma	Inhibition of the Wnt pathway	[12]
	Rh2	Skin cancer	Inhibition of autophagy-β-catenin pathway crosstalk	[13]
	Rk1, Rg5	Lung cancer	Inhibition of TGF-β1-induced EMT	[14]
Non-ginsenoside compounds	**Panaxynol**	Lung cancer	Inhibition of Hsp90	[15]

3.2.1. The Wnt/β-catenin pathway and ginseng-derived compounds

The Wnt/β-catenin pathway (also known as the canonical Wnt pathway) is delivered by Wnt ligand binding to Frizzled (FZD) receptors and the co-receptors low-density lipoprotein receptor-related protein 5 (LRP5) and LRP6, releasing β-catenin, activating its target gene expression [34] (Fig. 2). Since aberrant activation of the Wnt/β-catenin pathway was first identified in breast cancer, it has been identified in other types of cancer, and the Wnt/β-catenin pathway plays a crucial role in the maintenance of CSCs of various cancer types, including colon and cutaneous malignancies [67–69].

The inhibition of Wnt/β-catenin pathway by various types of ginsenosides has been observed in many studies, including cancer cells, adipocytes and normal stem cells [8,70–73]. In these studies, anti-proliferative or anti-migrative effects of ginsenosides in cancer cells were accompanied by reduced expression or transcription activity of β-catenin, suggesting possible the molecular mechanism will involve β-catenin stability. Moreover, ginsenosides were shown to inhibit EMT via Wnt/β-catenin inhibition, which suggests that ginsenosides not only exert the cytotoxic effect but also have potential to target CSCs. Indeed, ginsenoside Rb1 and its metabolite, compound K suppressed the ovarian CSC self-renewal and sensitized them to chemotherapy via Wnt/β-catenin inhibition. This study demonstrated that the combination of compound K and chemotherapeutics significantly reduced β-catenin expression accompanied by decrease in ABCG2 and P-glycoprotein, sensitizing cancer cells to chemotherapeutics [8]. ABCG2 and P-glycoprotein participate in the efflux chemotherapeutics and are known to be highly expressed in CSCs. Thus, this study supports the idea that ginsenoside-inhibited Wnt/β-catenin pathway can be more potent in the CSC population because they are more dependent on this pathway compared to non-CSCs. Rg3, one of the abundant ginsenosides in red ginseng, inhibited the Wnt/β-catenin pathway to inhibit the viability and self-renewal of patient-derived GBM stem cells [12]. Rh2, also an abundant ingredient in red ginseng, was shown to inhibit CSC in skin squamous cell carcinoma through affecting the crosstalk between autophagy and β-catenin pathway [13].

What is promising about the Wnt/β-catenin pathway regulation by ginsenosides is that the inhibition of this pathway is not detrimental to normal cells which underscores the low toxicity of ginsenosides as a drug candidate. In adipocytes, the Rb1 inhibited the Wnt/β-catenin pathway and this facilitates browning in white adipose tissue [73], which can be protective from the obesity. In terms of neural stem cell regulation, inhibition of Wnt/β-catenin pathway by Rg1 delayed brain senescence [72].

3.2.2. The Notch pathway and ginseng-derived compounds

The Notch pathway, comprising receptors (Notch) and ligands (Delta-like, DLL or Jagged), plays a crucial role in cell-cell communication, where the cleavage of the transmembrane subunit in Notch receptor is initiated by the ligand from adjacent cells [74]. This process is sequentially catalyzed by ADAM-family metalloproteinases and γ-secretase, releasing the transcriptional regulator Notch intracellular domain (NICD) [34,74] (Fig. 3). The abnormal activation of Notch has been linked to both hematopoietic and solid tumors [75], and it has also been demonstrated to be essential for maintaining CSCs. Sansone et al. demonstrated that IL6 stimulated the Notch3-dependent upregulation of Notch ligand, thereby inducing malignant stem/progenitor cells from human ductal breast carcinoma [76], and that the interaction between p66Shc and Notch3 promotes the self-renewal of mammary gland stem/progenitor cells under hypoxia [77]. The Notch inhibitor inhibited neurosphere formation and tumor initiation in vivo, accompanied by a reduction in the expression of putative CSC markers in glioblastoma

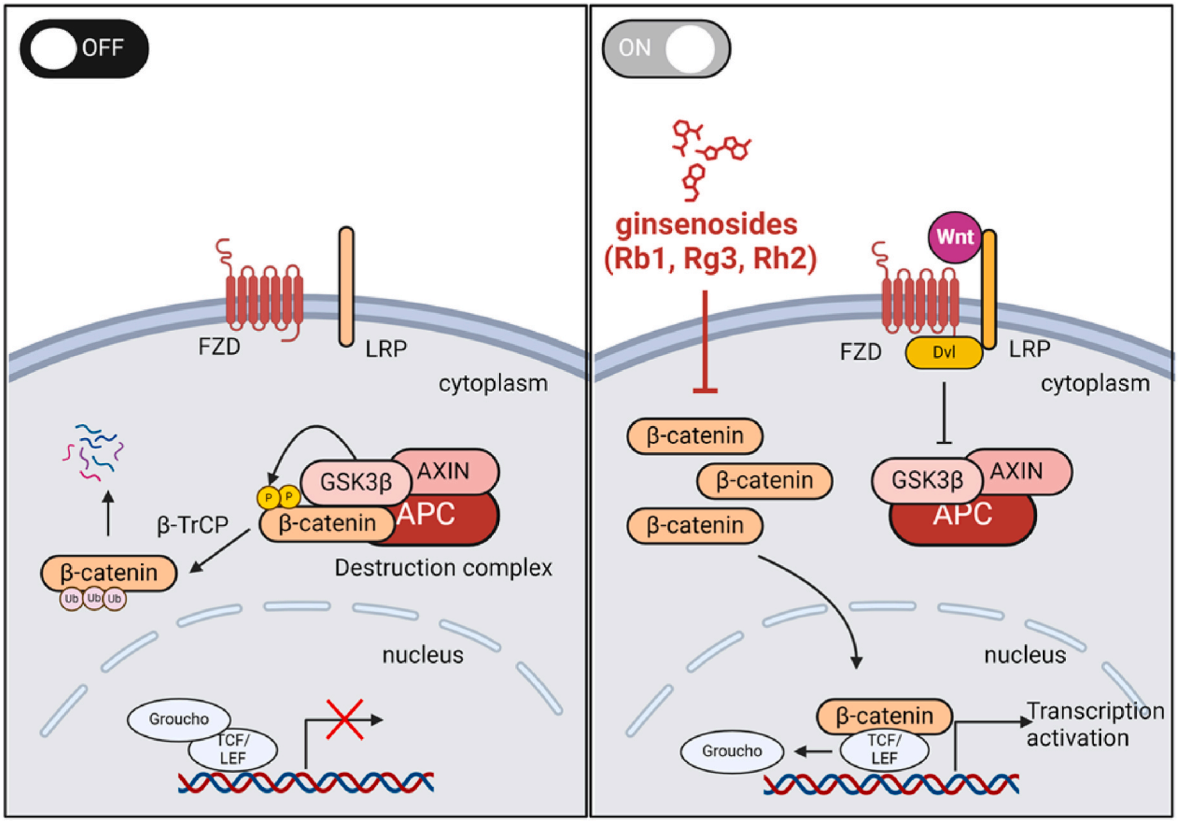

Fig. 2. The Wnt/β-catenin pathway. In the absence of Wnt ligands, the AXIN, GSK-3β, and APC degradation complex phosphorylates β-catenin and β-TrCP ubiquitinates β-catenin, resulting in proteasome-mediated degradation. A repressive complex (TCF/LEF and Groucho) represses target genes in the absence of β-catenin. When Wnt ligands bind to the Wnt receptor (FZD) and its co-receptor (LRP), β-catenin is liberated from the degradation complex and translocates to the nucleus, where it replaces Groucho and forms an active complex with TCF/LEF to activate the target genes. Ginsenosides (Rg1, Rg3, Rh2) decrease the protein level of β-catenin.

[78].

It has been reported that many of ginsenoside-induced pharmacological effects is mediated by Notch pathway [79,11]. In liver, the binding between Rg5 and SIRT1 was observed and this activated the SIRT1, a negative regulator of Wnt, inhibiting hepatic lipid accumulation and oxidative stress [79]. This study showed that Rg5 effect on modulating lipid metabolism and delaying the progression of non-alcoholic steatohepatitis (NASH), which also indicates the potential of inhibiting cancer progression. Song et al. demonstrated that Rg3 modulated myeloid derived suppressor cell (MDSC) in regulating EMT and cancer stemness of breast cancer cells. They showed that MDSC stimulated STAT3 and Notch pathway to support CSCs and Rg3 blocked the MDSC-mediated signaling activation in cancer cells [11]. While it is possible that Rg3 may modulate MDSC regardless of the Notch pathway, this study demonstrates that ginsenoside also participates in the indirect regulation of Notch pathway in cancer cells. Besides, this study confirms previous findings that MDSCs confer stem-like properties on breast cancer cells via crosstalk between the STAT3 and Notch pathways [80].

3.2.3. *The Hh pathway and ginseng-derived compounds*

Patched (PTCH) and Smoothened (SMO) are the primary constituents of the Hedgehog (Hh) pathway [81]. PTCH is a 12-span transmembrane protein that functions as the receptor for the Hg ligand, whereas SMO is a 7-span transmembrane protein that functions as the obligatory signal transducer [81]. In the absence of Hh ligand, PTCH represses SMO by inhibiting the transcription of target genes by the repressor form of GLI, GLI^R. Hh binding to PTCH represses the suppression on SMO by inhibiting the production of GLI^R and generating GLI^A, the activator form of GLI [81]. This cascade results in the translocation of GLI into the nucleus and the activation of its target genes (Fig. 4). The Hh pathway is involved in embryonic development and adult tissue homeostasis by modulating cell fate and proliferation; its dysregulation contributes to human disorders, such as congenital malformations [82]. In numerous malignancies, activating mutations or increased responses to Hh ligands have been observed to activate the Hh pathway [34,81]. Activation of the Hh pathway increases the expression of pluripotency genes including *NANOG*, *BMI1*, and *SOX*, thereby promoting the survival of CSCs in cancer [83,84]. SMO expression and its activity were highly enriched in the stem cell compartment of multiple myeloma, and blocking the Hh pathway inhibited the clonal expansion of the stem cell population without affecting the growth of malignant plasma cells [85].

Although the connection between ginsenosides and Hh pathway has not been extensively studied yet, there are some observations in lung cancer models. Rh2 inhibited the proliferation and expression of epithelial markers in lung cancer cells and further decreased the expression of genes related in Wnt or Hh pathways. Proteomic analysis revealed that the inhibition of Hh pathway by Rh2 is mediated by activating α-catenin, inhibiting the accumulation of β-catenin and GLI [86]. Rg3 also inhibited the proliferation, migration and invasion of lung cancer cells by inhibiting the Hh pathway with the observation of increased PTCH1 and decreased GLI1. In this study, Rg3 was shown to stably bind to PTCH1 through the molecular dynamics simulation, suggesting the potential molecular target of Rg3 [87]. These studies did not demonstrate whether ginsenosides directly inhibit CSCs, therefore ginsenosides' CSC-targeting activity via Hh pathway needs to be further investigated.

3.2.4. *Additional pathways involved in CSCs and ginsenosides*

Ginsenosides has been shown to be involved in additional pathways,

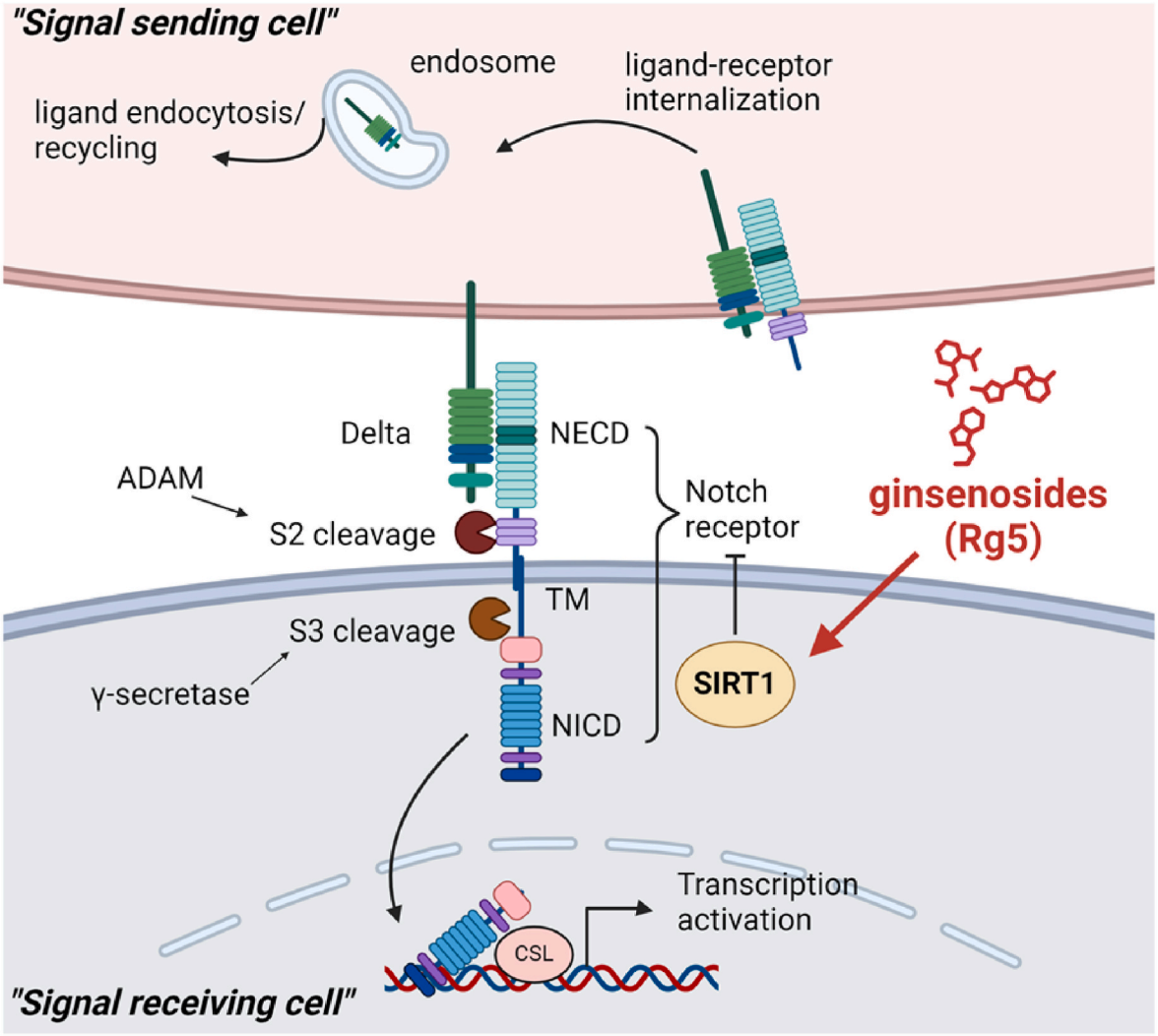

Fig. 3. The Notch signaling pathway. Notch pathway activation occurs when Notch ligand (Delta) expressed in signal-sending cells interacts with the Notch receptor, which contains extracellular (NECD), transmembrane (TM), and intracellular (NICD) domains. In signal-receiving cells, ligand-receptor binding induces the sequential proteolytic cleavage of NICD by ADAM and γ-secretase. The NICD translocates to the nucleus and attaches to the CSL transcription factor complex, thereby stimulating transcription of Notch target genes. Signal-sending cells maintain ligand-NECD binding and internalize it, followed by ligand endocytosis or recycling. Ginsenoside Rg5 binds to SIRT1, activating its negative regulator of Notch.

including nuclear factor-κB (NF-κB), Janus-activated kinase/signal transducer and activator of transcription (JAK-STAT), and phosphatidylinositol 3-kinase (PI3K)/Akt pathways, which also participate in supporting CSCs [88]. The activation of NF-κB pathway has been observed in CSC population of glioblastoma, breast cancer, and prostate cancer [89,90], and it is responsible for the transcription of CSC-related markers such as Oct4 and Sox2 [91,92]. Rg3 inhibited the hypoxia-induced NF-κB pathway [9] and Rg3-inhibited NF-κB sensitized colon cancer cells to conventional chemotherapies, such as docetaxel, paclitaxel, and cisplatin [93]. Rh1 inhibits the transcriptional activity of NF-κB and its combination with either STAT3 or NF-κB synergistically suppressed the migration of breast cancer cells [94]. Rk1 and Rg5, relatively less studied ginsenosides, also blocked the EMT process induced by TGF-β1, leading to a decrease in the CSC population in lung cancer [14].

The PI3K/Akt pathway controls numerous cellular physiologic phenotypes, including proliferation, survival, growth, and metabolism [95]. Its association with CSCs has also been observed in a variety of cancer types, and this suggests that the growth factor receptor signaling pathway may play a role in regulating CSCs, as the PI3K/Akt pathway is the main downstream of growth factor receptors [95]. In breast cancer models, insulin receptor substrate-2 (IRS2) promoted self-renewal in an PI3K pathway-dependent manner, connecting insulin/IGF and PI3K pathway-related CSC regulation [96]. The roles of ginsenosides in PI3K pathway have been supported by many studies [97], especially anticancer effects of Rg3 were shown to be accompanied by PI3K/Akt pathway inhibition. Rg3 inhibited the population of CSCs, self-renewal activities, and expression of CSC markers in breast cancer cell lines, which was accompanied by PI3K pathway inhibition [10]. In addition, an increase in the nuclear accumulation of hypoxia-inducible factor (HIF)-1α was observed in the mammospheres, which was disrupted by Rg3 [10]. HIFs have been suggested as a stem cell marker in a wide variety of cancer cells [98], therefore, investigation of the possible function of HIF-1α in CSCs and the mechanism underlying the Rg3-mediated HIF-1α regulation would provide the mechanism by which Rg3 targets CSCs.

3.2.5. *CSC-targeting activities of non-saponin components*

Due to their uniqueness to ginseng species, most research on the pharmacological effects of ginseng has focused on saponins; however, ginseng also contains numerous non-saponin components [58]. The physiological activities of these compounds, which include

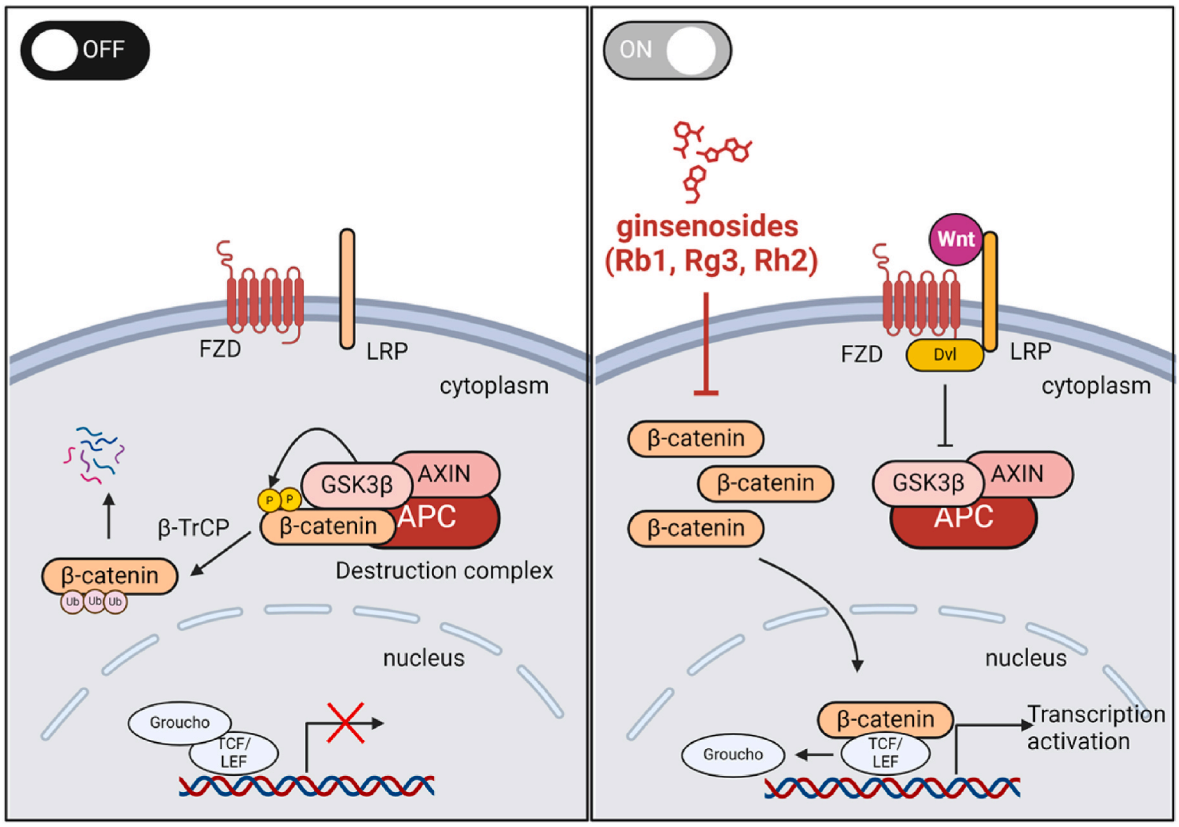

Fig. 4. The Hh signaling pathway. When the Hh pathway is inactive, PTCH inhibits SMO, thereby preventing the production of active GLI (GLI^A). GLI proteins are additionally sequestered by KIF7 and SUFU, partially degraded by E3 ubiquitin ligase, β-TrCP, and phosphorylated by PKA, GSK-3β, and CK1 to generate the repressor GLI (GLI^R). The repressor GLI accumulates and inhibits Hh target gene transcription. Sonic hedgehog (Shh), Indian hedgehog (Ihh), and delta hedgehog (Dhh) are Hh ligands in mammals. When Hh ligands bind to PTCH and co-receptors CDO, BOC, and GAS1, SMO facilitates the production of GLI^A, which then activates the transcription of Hh target genes. Ginsenoside Rg3 stably binds to PTCH, inhibiting the activation of SMO. Rh2 and Rg3 inhibits accumulation of GLI^A.

polysaccharides, proteins, peptides, amino acids, nucleic acids, alkaloids, polyacetylenes, phenolic compounds, essential oils, and phytosterols, are well described in a review article by Hyun et al. [58].

The antitumor activity of these non-saponin components has been reported [56,99,15]. Red ginseng polysaccharides inhibited the proliferation of breast and lung cancer cells by inducing ferroptosis and reducing the expression of GPX4, an enzyme that protects cells from membrane lipid peroxidation [99]. Panaxydol, a polyacetylene-class component, induced apoptosis, which was mediated by EGFR activation and ER stress [56]. Although research on the anticancer effect of non-saponin components is still in its infancy, one study demonstrated their potential as CSC-targeting molecules [15]. Panaxynol inhibited the self-renewal of both chemosensitive and chemoresistant non-small cell lung cancer cell lines [15]. Moreover, oral administration of panaxynol significantly inhibited the initiation and progression of lung cancer in a mutant Kras-driven spontaneous tumor model in mice, underscoring the clinical significance of this finding [15]. According to investigations at the molecular level, panaxynol exerts its bioactivity by binding to heat shock protein 90 (Hsp90) [15]. The significance of the heat shock protein (HSP) system in the regulation of CSCs has not been thoroughly explored prior to this research. Given that the HSP system is the essential apparatus for regulating the conformational maturation and stability of diverse proteins, including oncoproteins, the HSP system may play a role in maintaining the self-renewal capacity of CSCs [100]. This study suggests that the HSP system is a novel cellular target for the development of anti-CSC agents using various resources, including ginseng.

4. Limitations and future perspectives

The application of ginseng in therapeutics has taken a tremendous stride with accumulating research on the pharmacological activities of ginseng-derived compounds, and its use in modern medicine appears very close to actuality, particularly in anti-cancer therapies. Nonetheless, there are constraints that must be considered. First, prior to identifying the target, a more comprehensive mechanistic investigation must be conducted. Although research has made progress in understanding the role of each type of ginseng-derived compound in attenuating cancer progression, the detailed molecular mechanism underlying the pharmacological activities of these compounds still needs more vigorous research. Therefore, future research should focus on identification of molecular target of ginseng-derived compounds, which will enable predicting adverse effects and determining the therapeutic window. Secondly, the cytotoxic effect and self-renewal-suppressing effect should be separated, particularly in the context of CSC-targeting. For instance, the tumorsphere formation assay, which is the most widely used experiment for evaluating self-renewal, can be affected by the cytotoxic effect; thus, multiple methods are required to confirm the CSC-targeting effect. Other in vitro assays, such as surface expression of CSC markers and enzymatic activity of ALDH, and additional in vivo experiments, such as tumor-initiating potential or a tumor-relapse model, will strongly support the CSC-targeting activity of the compound. And for the clinical relevance, establishment of screening system using patients-derived samples will also powerfully demonstrate the therapeutic potential of ginseng-derived compounds. Lastly, ginseng research must receive greater international attention. Major investigations on ginseng-derived compounds are restricted to East Asia, where ginseng has been

used in traditional medicine for centuries. To bridge the gap between scientific knowledge and drug development, the pharmaceutical industry will be interested in more global research on ginseng.

5. Conclusions

Despite a few limitations, the anticancer potential of ginseng-derived compounds is enormous. The greatest advantage of ginseng is its proven safety. It is true that the safety of ginseng extract and each individual compound is not identical, but researchers have predicted relatively low toxicity based on a number of studies demonstrating minimal cytotoxic effects on normal cells. Also promising is the synergistic effect when combined with conventional chemotherapy. This has been observed in several studies in relation to regulating cancer stemness, suggesting that ginseng-derived compounds can provide therapeutic strategy for cancer with low response to conventional treatments. Although additional mechanistic research is required, ginseng can be used as a supportive therapy for patients. In addition, the CSC-targeting effect of these compounds on a wide variety of malignancies suggests that they could be used to treat various types of cancer. This is due to a variety of molecular mechanisms associated with their activity and the diversity of compound types. Therefore, the anticancer effects of ginseng-derived compounds have been demonstrated by many preclinical studies, and future research will require a greater comprehension of the mechanism of action for their use as anticancer agents.

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Conflicts of interest

The authors have declared that no conflict of interest exists.

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