# Unveiling the experimental proof of the anticancer potential of ginsenoside Rg3 (Review)

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**Abstract.** Ginsenoside Rg3 (GS-Rg3), a sterol molecule isolated from ginseng, has demonstrated various immunological properties, including inhibition of cancer cell proliferation and metastasis, reversal of drug resistance and enhancement of chemotherapy sensitivity. The recent surge in attention towards GS-Rg3 can be attributed to its potential as an antitumor angiogenesis agent and as a therapeutic candidate for immunotherapy. The development of GS-Rg3 as an agent for these purposes has accelerated research on its mechanisms of action. The present review summarizes recent studies investigating the antitumor activity of GS-Rg3 and its underlying mechanisms, as well as providing essential information for future studies on GS-Rg3.

**Contents**



## 1. Introduction

As the main active ingredient of an ancient Chinese herb that has been widely proven to be effective in cancer treatment, some related reviews have summarized the pharmacological effects of ginsenoside Rg3 (GS-Rg3) (1-4). With more in-depth research in recent years, more anticancer mechanisms of GS-Rg3 continue to be discovered. Therefore, the present article reviews the newly discovered anticancer mechanisms of GS-Rg3, aiming to highlight the current challenges and future prospects of GS-Rg3 in the field of cancer therapy.

GS-Rg3 is a tetracyclic triterpene saponin derived from red ginseng. Due to the chiral nature of C20, GS-Rg3 exists in two isomers: 20 (S) and 20 (R), the chemical structures of which are depicted in Fig. 1. Both 20(S)-GS-Rg3 and 20(R)-GS-Rg3 are white amorphous powders. The former is soluble in cold $H_2O$, ethanol, methanol and acetonitrile, while the latter is only soluble in DMSO, with trace amounts being soluble in $H_2O$ and acetonitrile (5).

$Fe@Fe_3O_4$ nanoparticles have been linked with GS-Rg3 to produce a nanodrug, NpRg3, which has been found to prolong the survival time of mice with dimethylnitrosamine-induced liver cancer (6) and to exhibit synergistic effects with anticancer drugs (7). These studies have demonstrated that GS-Rg3 has the potential to serve as a precursor for developing derivatives with enhanced therapeutic efficacy.

## 2. Antitumor effects of GS-Rg3

*Inhibition of tumor vascular endothelial cell proliferation.* Rapidly growing tumor cells experience a constant deprivation of oxygen and nutrients, necessitating the development of new vascular networks to sustain their growth. Angiogenesis, the formation of new blood vessels, occurs when endothelial progenitor cells (EPCs) or bone marrow-derived hematopoietic cells are recruited to the tumor (8). EPCs play a crucial role in early tumor growth by inhibiting angiogenic switches while simultaneously releasing angiogenic molecules to promote tumor neovascularization (9). Tumor cells secrete large amounts of pro-angiogenic substances to promote the growth of new vascular networks, which often results in the formation of immature, disorganized and leaky blood vessels. These aberrant blood vessels contribute to disease progression and increase resistance to therapy (10). GS-Rg3 can inhibit the proliferation of tumor vascular endothelial cells in two ways. First, it attenuates the Akt/endothelial nitric oxide synthase signaling pathway, which is dependent on vascular growth factors, and inhibits vascular progenitor cell migration and angiogenesis, thereby inhibiting the differentiation of EPCs and the formation of tumor blood vessels (11). Second, it blocks the PI3K/Akt and ERK1/2 pathways, which reduces the expression of vascular endothelial growth factor (VEGF) and

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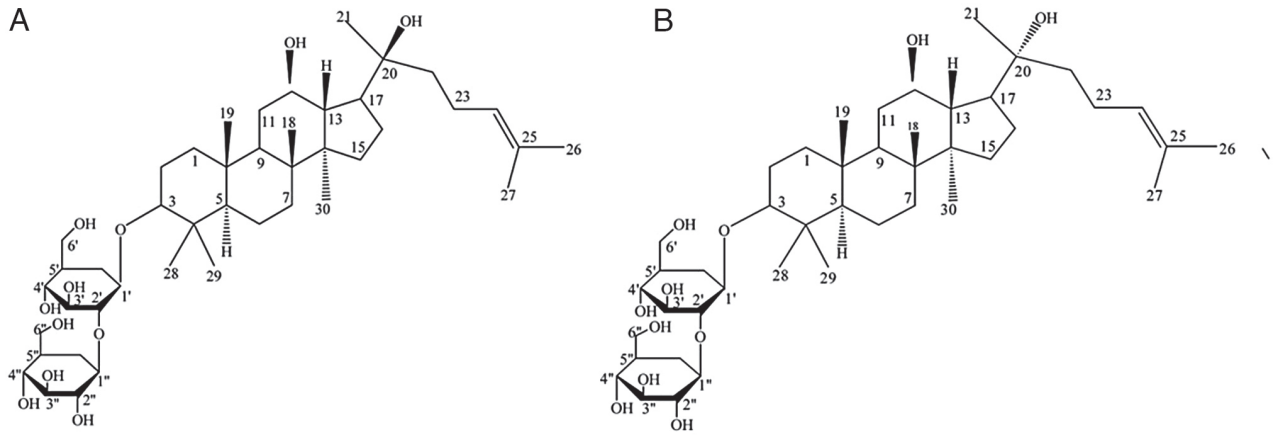


Figure 1. Two isomers of GS-Rg3, (A) 20(S)-GS-Rg3 and (B) 20(R)-GS-Rg3. GS-Rg3 has two enantiomers due to the chiral nature of C20. There are certain differences in the antitumor activities of the two isomers due to the different configurations. GS-Rg3, ginsenoside Rg3.

hypoxia-inducible factor (HIF)-1α at the mRNA and protein levels of bone marrow stromal cell (12).

*Inhibition of the production of vasculogenic mimicry (VM).* In 1999, Maniotis *et al* (13) reported that melanoma develops ducts that facilitate tumor perfusion but the VM typically associated with the vascular endothelium was not observed. VM has been found in various types of cancer, including melanoma (14), adrenal cortical carcinoma (15), lung cancer (16), glioma (17), colorectal cancer (18) and breast cancer (19). Anti-VM treatment has emerged as a promising antitumor target to reduce tumor cell blood perfusion (20).

*In vitro* studies have demonstrated the GS-Rg3 inhibits vascular endothelial cadherin (VE-cadherin), epithelial cell kinase and matrix metalloproteinase (MMP), leading to decreased angiogenesis stimulation in nude mice tumor xenografts and pancreatic cancer cells (21). To reduce VM development, it is recommended to inhibit the expression mRNA associated with the Wnt/β-catenin pathway, decrease the level of β-catenin in the nucleus and promote GSK-3β mRNA expression and β-catenin phosphorylation (22).

*Induction of cancer cell death.* Cells can undergo various types of death in response to pathological or physiological stimuli, including apoptosis, autophagy, cell necrosis, iron death and pyrolysis. While excessive cell death can be detrimental in certain contexts, cancer cells exhibit uncontrolled proliferation and growth rates that render the promotion of cell death a therapeutic goal in the treatment of neoplastic diseases.

Table I highlights the ability of 20(S)-GS-Rg3 to trigger apoptosis by various mechanisms, including mediation of the mitochondria, reactive oxygen species (ROS) production, degradation of the mitochondrial inner membrane and the release of apoptosis-inducing factor from mitochondria to the cytosol and the nucleus (23). Moreover, GS-Rg3 can impede the PI3K/Akt signaling pathway (24) and lower the methylation level of the promoter region of the p53, p16 and human mutL homolog 1 (hMLH1) genes, thereby promoting cell death in lung and ovarian cancer cells (25). Additionally, GS-Rg3 downregulates the expression of a long non-coding RNA, ATXN8OS, that represses tumor-suppressive microRNA (miR)-424-5p, facilitating tumor cell death (26). These findings suggest that GS-Rg3 holds potential as a potent therapeutic agent for cancer treatment.

*Inhibition of tumor metastasis.* Tumor metastasis is a leading cause of mortality in individuals with tumors. Previous studies have linked tumor metastasis to various factors, including E-cadherin, HIF, tumor-associated macrophages, retinoid acid receptor responder 3, and exosomes carrying miRNA (27,28). Notably, research has shown that GS-Rg3 can impede tumor cell metastasis by inhibiting the Wnt/β-catenin pathway (29). Additionally, GS-Rg3 inhibits the expression of nuclear factor κB (NF-κB), c-Myc, cyclooxygenase-2 and MMP-9, all of which are regulated by NF-κB (30). These findings suggest that GS-Rg3 has the potential to act as a potent therapeutic agent for preventing tumor metastasis.

*Inhibition of cell proliferation.* GS-Rg3 exhibits a significant effect on cancer cell proliferation. A previous study demonstrated that 20(R)-GS-Rg3 effectively inhibits tumor cell proliferation by increasing the levels of IL-2 and IFN-γ (31). 20(R)-GS-Rg3 can also upregulate Rho GTPase activating protein 9, which is implicated in cell proliferation and metastasis, to impede tumor cell proliferation (32). Furthermore, GS-Rg3 activates the VRK1/tumor protein p53 binding protein 1 pathway, thereby preserving DNA integrity and inhibiting non-small cell lung cancer cell proliferation (33). GS-Rg3 can also arrest A549 cell proliferation by halting the cell cycle at the G0/G1 phase through the EGFR/Ras/Raf/MEK/ERK pathway (34). Additionally, by inhibiting the expression of miR-4425 via the tumor suppressor gene, farnesyl-diphosphate farnesyltransferase 1 (35), GS-Rg3 reduces the methylation of p53, p16 and hMLH1 promoter regions, promotes their mRNA and protein levels and restricts ovarian cancer cell proliferation (25). Moreover, GS-Rg3 can suppress PC3 prostate cancer cell proliferation by arresting the ROS-mediated cell cycle (36,37). These findings suggest that GS-Rg3 has promise as a potent therapeutic agent for inhibiting cancer cell proliferation. By contrast, GS-Rg3 can stimulate cell proliferation even at low concentrations through the mTORC1 pathway and mitochondrial biogenesis (38).

Table I. Summary of the anticancer activities of GS-Rg3.

| First author/s, year | Cancer type | Test subjects | Effects | Mechanism | (Refs.) |
|---|---|---|---|---|---|
| Zeng *et al*, 2014 | Acute leukemia | Bone marrow stromal cells; randomized patients | Inhibited angiogenesis | Inhibited the PI3K/Akt and ERK1/2 pathways and suppressed the expression of VEGF and HIF-1α at the mRNA and protein levels in bone marrow stromal cells | (12) |
| Mao *et al*, 2020 | Osteosarcoma | MG63 and 143B cells | Inhibited metastasis, proliferation and invasion | Reduced the expression of MMPs, suppressed the expression of epithelial-mesenchymal transition markers and inhibited activation of the Wnt/β-Catenin signaling pathway | (29) |
| GUO *et al*, 2014 | Pancreatic cancer | PANC-1, SW1900, Bxpc-3 and MiaPaCa-2 cells; BALB/c mice | Inhibited vasculogenic mimicry | Reduced VE-cadherin, EphA2 and MMP expression | (21) |
| Wu *et al*, 2014 | Liver cancer | H22 cells; SPF mice | Inhibited tumor proliferation and enhanced immunity | Increased IL-5 and IFN-γ levels. The effect of 20(R)-Rg3 was significantly greater than that of 20(S)-Rg3 ($P<0.05$) | (31) |
| Sun *et al*, 2019 | Liver cancer | HepG2 and MHCC-97L cells; BALB/c mice | Inhibited metastasis and proliferation | Increased expression of ARHGAP9 | (32) |
| Junmin *et al*, 2015 | Colon cancer | SW480 cells | Inhibited metastasis | Inhibited the expression of NF-κB and the expression of c-Myc, COX-2 and MMP-9 that was regulated by NF-κB | (23) |
| Tang *et al*, 2018 | Colorectal cancer | SW620 and HCT116 cells | Inhibited proliferation and migration | Downregulated 22 pro-angiogenic genes (ANGPT1, ANGPT2, CCL13, COL18A, CSF3, CXCL1, EGF, FGF-2, IL1A, IL1B, IL8, KDR, MMP1, PGF, PIGF, PLAUR, TEK, THPO, TIMP1 and TIMP2) | (85) |
| Bian *et al*, 2019 | Cervical cancer | HeLa cells | Induced apoptosis | Caused mitochondrial-mediated apoptosis, production of ROS, degradation of the mitochondrial membrane, the release of AIF from the mitochondria and nuclear translocation | (30) |
| Xie *et al*, 2017 | Lung cancer | A549 and H23 cells; nude mice | Induced apoptosis and inhibited proliferation | Inhibited the PI3K/Akt pathway | (24) |
| Liu *et al*, 2019 | Lung cancer | A549 and HCC827 cells; C57BL/6 mice | Inhibited proliferation | Activated the VRK1/P53BP1 pathway and protected DNA integrity | (33) |
| Lu *et al*, 2020 | Ovarian cancer | SKOV3 and 3AO cells; BALB/c mice | Inhibited proliferation and metastasis | Downregulates expression of oncogenic miR-4425, which in turn upregulated the expression of tumor suppressor gene FDFT1, which is repressed by miR-4425 | (35) |
| Zhou *et al*, 2019 | Ovarian cancer | HOSEpiC and SKOV3 cells | Inhibited proliferation, invasion and metastasis, and induced apoptosis | Reduces methylation of p53, p16 and hMLH1 promoter regions, promotes the expression of their mRNA and proteins | (25) |
| Peng *et al*, 2019 | Prostate cancer | PC3 cells | Inhibited proliferation | Upregulates ROS-mediated cell cycle inhibition | (36) |

Table I. Continued.

| First author/s, year | Cancer type | Test subjects | Effects | Mechanism | (Refs.) |
|---|---|---|---|---|---|
| Kim *et al*, 2021 | Breast cancer | MCF-7 cells | Inhibited proliferation and inducted apoptosis | Decreased ATXN8OS, which inhibits the tumor suppressor gene, miR-424-5p | (26) |
| Song *et al*, 2020 | Breast cancer | FM3A cells; C3H/He mice | Inhibited the transformation of cancer stem cells and mesenchymal cells | Inhibited the STAT3 and NOTCH pathway | (86) |
| Ge *et al*, 2014 | Esophageal cancer | EC109, TE1 and KYSE170 cells | Increased radiation sensitivity | Decreased VEGF and HIF-1α expression | (87) |
| Qu *et al*, 2019 | Stomach cancer | BGC823 cells | Inhibited angiogenesis and proliferation | Decreased the expression of HIF-1α and VEGF | (88) |
| Liu *et al*, 2020 | Stomach cancer | Atp4a-/-C57Bl/6 mice | Reduced gastric precancerous lesions | Reduced abnormal glycolysis in mice with gastric precancerous lesions by regulating the expression of PI3K, Akt, mTOR, HIF-1α, LDHA, HK-II and miR-21 | (28) |

AIF, apoptosis inducing factor; ARHGAP9, Rho GTPase activating protein 9; COX-2, cyclooxygenase-2; EphA2, epithelial cell kinase; FDFT1, farnesyl-diphosphate farnesyltransferase 1; IFN-γ, interferon-γ; GS-Rg3, ginsenoside Rg3; HIF, hypoxia-inducible factor; HK, hexokinase; LDHA, lactate dehydrogenase A; miR, micro RNA; MMP, matrix metalloproteinase; NF-κB, nuclear factor κB; P53BP1, tumor protein p53 binding protein 1; ROS, reactive oxygen species; VE-cadherin, vascular endothelial cadherin; VEGF, vascular endothelial growth factor.

*Regulation of mitophagy*. Red ginseng-derived GS-Rg3 extract has been found to induce apoptosis and mitochondrial autophagy in lung cancer cells by producing ROS (39). In colorectal cancer, GS-Rg3 treatment exerts antitumor effects by activating the PTEN-induced kinase 1-Parkin signaling pathway, increasing the ubiquitination of GAPDH and promoting mitochondrial autophagy (40).

*Combination with other treatment*. GS-Rg3 can be synergistically combined with other treatments such as radiotherapy, chemotherapy and targeted therapy, to enhance its antitumor effects. For instance, combining GS-Rg3 with gefitinib can increase gefitinib efficacy in treating malignancy, as depicted in Table II. This combination can elevate the levels of anti-apoptotic protein, Bcl-2, pro-apoptotic protein, Bax, and caspase-3, while reducing the levels of migration-promoting factors, SNAIL and SLUG, and increasing the level of anti-migration protein, E-cadherin, thereby enhancing the pro-apoptotic effect on lung cancer cells and inhibiting metastasis (41). GS-Rg3 can also potentiate the efficacy of drugs in patients with advanced non-small cell lung cancer and reduce chemotherapy-induced drug toxicity (42). Furthermore, GS-Rg3 can reduce the cisplatin resistance of gastric cancer cells by upregulating miR-2 and inhibiting SRY-box transcription factor 3 and the PI3K/Akt/mTOR signaling axis (43). GS-Rg3 can also increase the sensitivity of pancreatic cancer to gemcitabine by decreasing ZFP91-mediated TSPY like 2 instability (44). Moreover, GS-Rg3 can enhance the radiosensitivity of cancer cells in different tumor types, such as lung, breast and nasopharyngeal cancer (45-47). Additionally, GS-Rg3 combined with artemisinin can inhibit STAT3 signal transduction in hepatocellular carcinoma cancer cells, synergistically reduce the viability of cells, induce apoptosis and inhibit the growth of mouse hepatocellular carcinoma (48). Similarly, the combined therapy of GS-Rg3 and sorafenib can mitigate the progression of hepatocellular carcinoma by inhibiting hexokinase 2-mediated glycolysis and the PI3K/Akt signaling pathway (49). Moreover, a meta-analysis has demonstrated that transarterial chemoembolization combined with GS-Rg3 can effectively enhance the objective response rate and disease control rate of hepatocellular carcinoma while reducing adverse reactions to treatment (50).

*Regulating non-coding RNA*. GS-Rg3 can modulate the expression of non-coding RNAs, such as miRNAs, circular (circ)RNAs and long non-coding RNAs, in various types of tumor types, thereby inhibiting tumorigenesis and progression by regulating the corresponding signaling pathways. For example, in hepatocellular carcinoma, GS-Rg3 can inhibit the PI3K/Akt signaling pathway by downregulating expression of the long non-coding RNA, HOTAIR, which inhibits the proliferation and metastasis of hepatocellular carcinoma (51).

Table II. Effect of GS-Rg3 combined with chemotherapeutic drugs.

| First author/s, year | Drug | Test subjects | Effects | Mechanisms | (Refs.) |
|---|---|---|---|---|---|
| Chang *et al*, 2014 | Paclitaxel + Cisplatin | EC109, TE1 and KYSE170 cells | Combination chemotherapy was more effective in inhibiting tumor growth than non-combination chemotherapy and reduced tumor microvessel density | Not investigated | (89) |
| Dai *et al*, 2019 | Gefitinib | A549 and H1299 cells | Increased the apoptosis of NSCLC cell lines and reduced the metastasis of cancer cells | Increased the expression levels of the pro-apoptotic protein, Bax, active caspase-3, the anti-migration protein, E-cadherin, and reduced the expression levels of the anti-apoptotic, protein Bcl-2, and pro-migration factors, SNAIL and SLUG | (41) |
| Lee *et al*, 2014 | Cisplatin | T24R2 cells | Inhibited the proliferation of cisplatin resistant bladder cancer cells | Ratio of drug-resistant cells in S phase and G2/M phase increased and the ratio in G0-G1 phase decreased; increased the expression of the pro-apoptotic protein, Bad, and cytochrome c; reduced Bcl-2c expression | (90) |
| Zou *et al*, 2020 | Gemcitabine | Panc-1 and SW1990 cells; BALB/c mice | Inhibited the growth of gemcitabine-resistant cells and induced apoptosis | Upregulated CASC2 and activated the PTEN signaling pathway | (91) |
| Ahmmed *et al*, 2019 | Gemcitabine | A549 and SPCA1 cells | Enhanced the cytotoxicity of gemcitabine and reduced the invasion effect of cancer cells | Inhibited NF-κB and downregulated the expression of PTX3 and p65 | (92) |
| Yuan *et al*, 2017 | Paclitaxel | MDA-MB-231, MDA-MB453 and BT-549 cells; BALB/c nu/nu mice | Promoted the cytotoxicity and induced the apoptosis effect of paclitaxel | Inhibited NF-κB signal transduction and regulated the expression of Bax/Bcl-2 in triple negative breast cancer | (93) |
| Li *et al*, 2017 | Doxorubicin | MDA-MB-231 doxorubicin resistant cells; SD male rats; C57/BL and BALB/c mice | Reduced cardiotoxicity and antagonized cancer cell resistance | Inhibited calcium permeability to maintain the homeostasis of the sarcoplasmic reticulum. The mechanism of antagonism drug resistance was not clarified | (94) |
| Shan *et al*, 2019 | Oxaliplatin | SMMC-7721 cells | Enhanced the antitumor effect, inhibited the proliferation of liver cancer cells and promoted apoptosis | Diminished the expression of PCNA and cyclin D1 | (95) |

CASC2, cancer susceptibility 2; NF-κB, nuclear factor κB; NSCLC, non-small cell lung cancer; PCNA, proliferating cell nuclear antigen; PTX3, pentraxin 3.

GS-Rg3 can impede osteosarcoma progression by modulating the circ_0003074/miR-516b-5p/karyopherin subunit α4 (KPNA4) axis. GS-Rg3 significantly reduces the expression of circ_0003074, elevates the expression of miR-516b-5p and downregulates the expression of KPNA4 (52). In breast cancer, GS-Rg3 can counteract the inhibitory effect of the oncogenic

long non-coding RNA, ATXN8OS, on the tumor suppressive miR-424-5p, thereby increasing apoptosis and inhibiting the proliferation of breast cancer cells (26). Furthermore, GS-Rg3 can exert antitumor effects on ovarian cancer by inhibiting expression of the long non-coding RNA, H19, which impedes the proliferation, migration and invasion of ovarian cancer cells (53). These findings suggest that GS-Rg3 is a promising therapeutic agent for modulating non-coding RNAs and thus regulating the corresponding signaling pathways to inhibit tumorigenesis and tumor progression.

*Reversing the tumor microenvironment (TME).* The TME plays a crucial role in tumor proliferation, metastasis and response to therapy. Typically, immune suppression mediated by the TME leads to poor antitumor responses to therapy (54). However, GS-Rg3 can exert antitumor effects by modulating the TME. Current research in this area is primarily focused on breast cancer. Innovative drug delivery modalities such as GS-Rg3-based liposomes, can achieve targeted localization to human breast cancer paclitaxel-resistant cells and their TME, resulting in the repolarization of M2 macrophages from a tumor-promoting phenotype to an antitumor M1 phenotype. Through dual action of targeting tumor cells and remodeling the TME, to 90.3% of paclitaxel-resistant breast cancer cells are killed (55). In addition to paclitaxel, GS-Rg3-based liposomes can significantly enhance the antitumor effects of docetaxel in triple-negative breast cancer (56). Moreover, GS-Rg3-modified nanoparticles can enhance the immunogenic cell death (ICD) effect induced by doxorubicin (57). When combined with programmed death-ligand 1 (PD-L1) blockade, significant antitumor effects can be achieved in breast cancer through the recruitment of memory T cells and decreased adaptive PD-L1 enrichment (57). For lung metastases, the combination of GS-Rg3-based liposomes with chemotherapy drugs allows for improved capture of circulating tumor cells. Upon reaching the lungs, the immunosuppressive microenvironment is reversed, leading to the inhibition of breast cancer lung metastasis (58). Paclitaxel-loaded GS-Rg3-based liposomes can activate the immune microenvironment in glioblastoma, expanding the population of CD8 T cells to promote T cell immune responses, increasing the M1/M2 ratio and reducing the number of regulatory T cells and myeloid-derived suppressor cells, significantly prolonging the survival time of mice with glioblastoma (7). Furthermore, GS-Rg3 and quercetin nanoparticles can enhance tumor targeting in colorectal cancer mice, with GS-Rg3 serving as an inducer of ICD. This allows for the recruitment, activation, migration and cross-presentation of antigen-presenting cells in lymph nodes and tertiary lymphoid tissues, markedly modulating the immunosuppressive TME, and remodeling 'cold' (non-T cell-inflamed) tumors into 'hot' (T cell-inflamed) tumors (59). These findings suggest that GS-Rg3-based drug delivery systems remodel the TME and enhance antitumor effects by reversing immune suppression, activating immune responses and promoting ICD.

## 3. Preparation of nanomedicines

Various types of ginsenoside nanomedicines have shown potential in the treatment of different tumors, including triple-negative breast cancer (60). The *in vivo* delivery results of a multifunctional black phosphorus (BP) nanoreagent, BPs/G-Rg3@PLGA, demonstrated its notable therapeutic effect on lung metastases from breast cancer, along with significant biocompatibility with various organs/tissues (61). GS-Rg3-loaded carbon nanotubes have been shown to reduce IFN-γ-induced upregulation of PD-L1 in breast cancer cells, thereby decreasing the programmed cell death protein-1/PD-L1 axis in the T cell/triple-negative breast cancer cell coculture system (62). GS-Rg3 loaded on a biomimetic nanosystem has been shown to enhance the sensitivity of tumors to doxorubicin, thereby initiating antitumor immune activation and effectively combating leukemia cells harbored in the bone marrow (63). Nanoparticles constructed using graphene oxide (GO) linked with the photosensitizer, indocyanine green (ICG), folic acid and polyethylene glycol (PEG), and loaded with GS-Rg3 (PEG-GO-FA/ICG-Rg3) can inhibit the proliferation, invasion and migration of osteosarcoma cells, enhance the apoptosis and autophagy of osteosarcoma cells and suppress the stemness of osteosarcoma cell-derived cancer stem cells (64). Ursolic acid and GS-Rg3 co-loaded liposomes can significantly reduce the proliferation of liver cancer cells, while increasing the apoptotic rate and the proportion of cells in the G0/G1 phase (65). A novel nanomedicine was recently developed by combining metal-based nanoenzymes (Fe@Fe3O4) with GS-Rg3. The glycosidic chains of GS-Rg3 formed a hydrophilic layer on the outermost surface of the nanomedicine, improving biocompatibility and pharmacokinetics, thus promoting the apoptosis of cancer cells (66). These studies suggest that ginsenoside nanomedicines have great potential in the treatment of a variety of tumor types, with improved biocompatibility, targeted delivery and enhanced therapeutic efficacy.

## 4. Immune regulation

A number of extracts from Chinese medicinal herbs are used to treat immunological issues, and immune modulation is a key mode of action of GS-Rg3. GS-Rg3 enhances cellular immunity by upregulating $CD4^+$, $CD4^+/CD8^+$, IgG, IgM and IL-2, and downregulating $CD8^+$ and IL-6 in a dose-dependent manner (67). This effect may be related to its stimulation of concanavalin A (ConA)-induced lymphocyte proliferation and increased levels of the Type 1 T helper (Th1)-type cytokines, IL-2 and interferon (IFN)-γ (31). Furthermore, 20(R)-GS-Rg3 promotes natural killer (NK) cell activity via activation of the MAPK/ERK pathway, suggesting that 20(R)-GS-Rg3 may be used as an activator of NK cell cytotoxicity to treat various types of cancer (68). Cyclophosphamide decreases T-bet and IFN-γ expression in the thymus and spleen, while increasing GATA-3 and IL-4 expression, thereby altering the Th1/Th2 balance and resulting in immunosuppression (69). GS-Rg3 can antagonize this effect by regulating the ratio of T lymphocyte subsets (70). For autoimmune neuroinflammation, GS-Rg3 has a minor effect on the dendritic cell production of Th17-promoting cytokines such as IL-6, IL-12/23p40 and TNFα. Specifically, it upregulates the expression of TNFα and IL-12 and downregulates the expression of IL-6. Instead, it notably reduces the induction of RAR-related orphan nuclear receptor γt expression in the $CD4^+$ T cells, and therefore inhibits the differentiation of Th17 cells from their

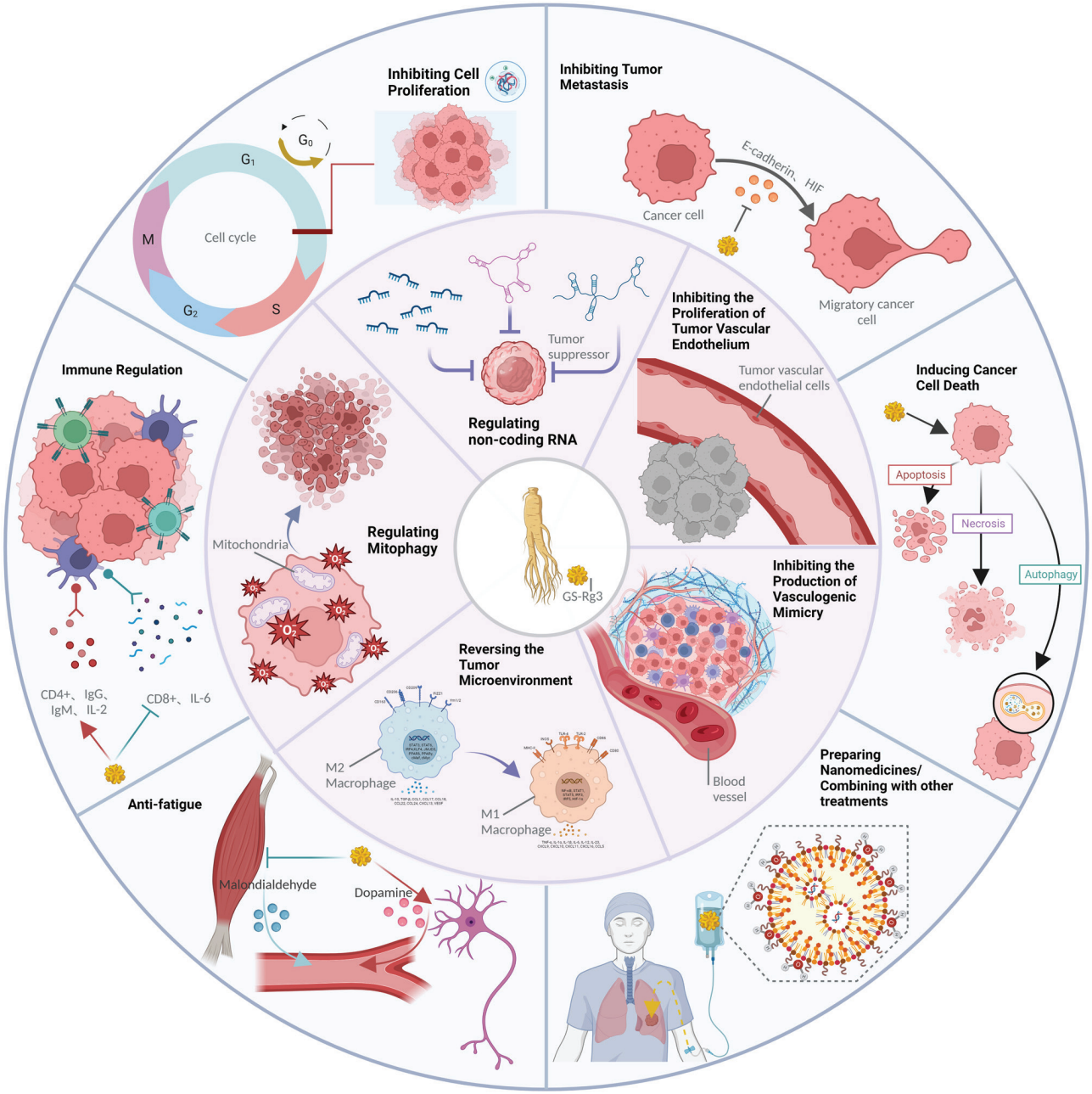


Figure 2. Diverse cancer-fighting mechanisms of GS-Rg3, a promising new anticancer agent. These mechanisms include induction of tumor apoptosis, inhibition of tumor metastasis, proliferation and angiogenesis, regulation of non-coding RNA, enhancement of immune function, reversal of inhibitory tumor microenvironments and promotion of mitochondrial autophagy. This also involved the preparation of novel nanomedicines. E-cadherin, endothelial cadherin; GS-Rg3, ginsenoside Rg3; HIF, hypoxia-inducible factor.

precursors (71). These finding suggest that GS-Rg3 may be a promising therapeutic agent for the treatment of Th17-related autoimmune disorders.

GS-Rg3 has two chiral isomers with notably distinct therapeutic properties. An investigation was conducted to compare the immunological response of 20(S)-GS-Rg3 and 20(R)-GS-Rg3 as adjuvants to ovalbumin (OVA). The results revealed that both 20(R)-GS-Rg3 and 20(S)-GS-Rg3 can serve as adjuvants for the immunological response induced by OVA. However, 20(R)-GS-Rg3 significantly increased OVA-specific IgG and IgG subtypes in the blood, relative to 20(S)-GS-Rg3, and was accompanied by a marked rise in serum IFN-γ and IL-5 levels (72). 20(R)-Rg3 significantly enhanced splenocyte proliferative responses to Con A, LPS and OVA as well as mRNA expression of IFN-γ, IL-12, IL-4 and IL-10 and transcription factors T-bet and GATA-3 by splenocytes when compared with the 20(S)-Rg3 (67).

## 5. Anti-fatigue effects of GS-Rg3

GS-Rg3 has anti-fatigue properties. GS-Rg3 can increase the physical strength of older rats by increasing serum total cholesterol, triglyceride and lactate dehydrogenase concentrations, increasing superoxide dismutase concentrations, decreasing malondialdehyde release in skeletal muscle and increasing phosphoenolpyruvate carboxykinase mRNA expression (73).

GS-Rg3 can also relieve the pain and discomfort associated with cancer and anti-cancer drugs, improving patient comfort (74,75). GS-Rg3 has also been found to stimulate sirtuin 1, which protects skeletal muscles from damage caused by reactive oxygen species and thus acts as an anti-fatigue agent (73). In rats, fatigue can decrease the production and phosphorylation of tyrosine hydroxylase, which results in a decrease in dopamine. GS-Rg3 has been shown to effectively reverse this by increasing the phosphorylation of synuclein, protein kinase A, ERK1/2 and Akt (76). These findings suggest that GS-Rg3 has potential as a natural anti-fatigue agent and may have beneficial effects in improving physical strength and relieving the pain and discomfort associated with cancer.

## 6. Final remarks

GS-Rg3 has emerged as a promising new anticancer agent with multifaceted and heterogeneous anticancer properties across various cancer types. Notably, GS-Rg3 has demonstrated therapeutic benefits in the treatment of liver, lung, gastric, breast, ovarian and prostate cancer. Recent literature reports have shed light on the diverse cancer-fighting mechanisms of GS-Rg3, including induction of tumor apoptosis, inhibition of tumor metastasis, proliferation and angiogenesis, enhancement of immune function, reversal of inhibitory TMEs and promotion of mitochondrial autophagy (Fig. 2). The use of immune checkpoint inhibitors has resulted in significant improvements in the treatment paradigm for various solid tumors, leading to notable enhancements in overall efficacy and patient prognosis (77). Nevertheless, the issue of resistance to immune therapy remains a significant challenge. Tumor cells exploit their inhibitory immune microenvironments to evade the effects of immune checkpoint inhibitors, a phenomenon that has been demonstrated by numerous studies to be reversible through the use of GS-Rg3. Ginseng, an ancient and valuable Chinese herbal medicine, has a notable impact on the immune system. The gut microbiota maintains a symbiotic relationship with the intestinal mucosa, which is the largest immune organ in the human body (78). Through the integration of environmental factors such as diet, with genetic and immune signals, the gut microbiota can influence the metabolism, immune function, neurodevelopment and pathogen colonization of the host. Similarly, alterations in the host immune environment can also impact the gut microbiota through different immune cells such as dendritic cells, regulatory T cells, monocytes, etc (79,80) Dysbiosis of the gut microbiota can result in changes in intestinal permeability, disrupting the existing equilibrium and affecting the metabolism and immune function of the host, thereby contributing to the development of various diseases, such as inflammatory bowel disease, depression, and cancer (80,81). In recent years, there has been increasing recognition of the importance of the gut microbiota in the diagnosis and treatment of diseases. As such, investigating whether the interaction between orally administered GS-Rg3 and the gut microbiota affects the anticancer effects of GS-Rg3 is a worthwhile endeavor.

Mitochondria, which serve as cellular energy factories, play a crucial role in cells, particularly cancer cells. Mitochondrial autophagy may exert a bidirectional regulatory effect on the occurrence and development of cancer; it can promote cancer progression by enabling cancer cells to survive under stress or it can induce carcinogenesis by affecting cell signaling transduction or promoting intracellular toxicity when mutations or abnormalities occur (82). Recent studies have also demonstrated that abnormal mitochondrial function is linked to the cellular immune response (83,84). At present, there are limited investigations regarding whether GS-Rg3 can influence cancer cell proliferation by modulating mitochondrial autophagy or other mitochondrial functions and activities. This area may be a future research focus to identify new properties that GS-Rg3 may offer in the field of antitumor therapy.

However, the low oral bioavailability of GS-Rg3, given its extensive pro-systemic metabolism and poor membrane permeability, prevents the attainment of high working concentrations *in vivo* (38). Given that reaching the concentration of GS-Rg3 required to inhibit cancer cell growth *in vivo* is challenging, efforts should also be focused on investigating new methods to improve the solubility of GS-Rg3 without decreasing the efficacy of the drug, such as in the development of cofactors to aid in solubilization. The combination of GS-Rg3 with cholesterol transport liposomes as an alternative approach has shown greater therapeutic efficacy, reduced toxicity and the potential for overcoming drug resistance, exhibiting certain synergistic effects with anticancer drugs (60). Additionally, GS-Rg3 has displayed functions that are independent of its anticancer effects, such as enhancing biocompatibility and pharmacokinetics, which offer new directions for its optimal utilization.

Overall, research in basic medicine has highlighted the marked anticancer properties of GS-Rg3 across various tumor types. However, its clinical use is predominantly restricted to primary lung cancer and liver cancer chemotherapy. The ongoing research efforts aim to fully harness the anticancer capabilities of GS-Rg3 within biological systems, potentially broadening its clinical applications to a wider range of cancer types. Meanwhile, more clinical trials should be conducted to comprehensively evaluate its safety and feasibility to realize its clinical application and benefits to patients. In summary, the evidence presented thus far suggests that GS-Rg3 is a promising anticancer agent that warrants further investigation. Further clinical trials are required to assess the effectiveness and safety of GS-Rg3 and optimize its potential for clinical implementation in cancer treatment.

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YZ edited the review. JN and GL wrote the review. YL was a major contributor in revision of the manuscript. All authors

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### Competing interests

The authors declare that they have no competing interests.

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