Molecular Biology Reports (2021) 48:2639–2652
https://doi.org/10.1007/s11033-021-06187-2

REVIEW

Insights into the antitumor mechanism of ginsenosides Rg3

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Received: 20 December 2020 / Accepted: 28 January 2021 / Published online: 4 March 2021

Abstract

Panax ginseng, an ancient herb, belonging to Chinese traditional medicine, is an important herb that has a remarkable impact on various diseases. Ginsenoside Rg3, one of the most abundant ginsenosides, exerts significant functions in the prevention of various types of cancers with few side effects. In the present review, its functional molecular mechanisms are explored, including the improvement of antioxidant and anti-inflammation properties, immune regulation, induction of tumor apoptosis, prevention of tumor invasion and metastasis, tumor proliferation and angiogenesis, and reduction of chemoresistance and radioresistance. On the other hand, metabolism, pharmacokinetics and clinical indications of Rg3 are also discussed. The biological functional role of ginsenoside Rg3 may be associated with that it is a steroid glycoside with diverse biological activities and many signaling pathway can be regulated. Many clinical trials are highly needed to confirm the functions of ginsenoside Rg3.

Keywords Ginsenoside Rg3 · Antitumor activities · Molecular mechanism · Tumor invasion and metastasis · Tumor proliferation and angiogenesis

Introduction

Panax ginseng, an ancient herb, belonging to Chinese traditional medicine, is an important herb that has clear effects on the treatment of diverse diseases [1–3]. Ginsenoside, a class of steroid glycosides, is one of the dominant secondary metabolites in ginseng and armed with various pharmacological activities [4–6]. Ginsenoside Rg3, one of the most abundant ginsenosides, has been explored in the prevention of inflammation [7], diabetes [8, 9], and cardiovascular diseases [10]. Cancer is the first cause of death followed by ischemic heart disease and stroke in the world [11]. The antitumor activities of ginsenoside Rg3 have been explored in many types of cancers, including the induction of apoptosis, inhibition of tumor growth, proliferation, metastasis invasion and angiogenesis, and cell cycle arrest (Table 1). In order to better understand its function in various anti-tumor activities, the related molecular mechanisms of Ginsenoside Rg3 in the prevention of various cancer risks were reviewed in the present paper.

Ginsenoside Rg3 improves anti-inflammatory capacity

Chronic inflammation plays a critical role in the development of various types of cancers, from initiation, progression to metastasis [12, 13] and worsens the outcomes of cancer patients. T cell cytokines are related to various clinical aspects of hepatocellular carcinoma (HCC), and interleukin (IL)-6 is the most suggestive predictor of survival [14]. Inflammatory cytokines including interferon-(IFN)-α, -β, and -γ; interleukin-(IL) -2, -6, and -10, and tumor necrosis factor (TNF)-α are all associated with breast cancer development [15].

Ginsenoside Rg3 has been proposed to ameliorate various inflammatory diseases in animal models, including T-cell-mediated inflammation diseases [16]. Rg3 can attenuate inflammatory status in a rat model by decreasing serum TNF-α, IL-1β and IL-6 levels and increasing serum IL-10 levels [17]. Further work indicates that ginsenoside Rg3 can attenuate lipopolysaccharide (LPS)-induced acute lung

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Table 1 Antitumor activity of ginsenoside Rb3

Tumor type	Cell lines	Antitumor activity	Mechanism	References
Osteosarcoma	MG-63, OS732, U-2OS and HOS	Induces apoptosis	Induces DNA damage	[103]
Breast cancer	MDA-MB-231	Induces apoptosis	An increase in the ratio of proapoptotic Bax to antiapoptotic Bcl-2, depolarization of the mitochondria membrane potential and the release of cytochrome c from mitochondria. Induces the proteolytic cleavage of caspase-3 and poly (ADP-ribose) polymerase	[104]
Breast cancer	MCF-7	Cytotoxicity and partial reversal of doxocubicin resistance		[105]
Breast cancer	MDA-MB-231	Inhibits proliferation and induces apoptosis	Blocks NF-κB signaling via inactivation of ERK and Akt	[106]
Breast cancer	MDA-MB-231	Inhibits of cancer migrations	Inhibits CXCR4 expression	[107]
Colon cancer	HT-29	Inhibits proliferation and induces apoptosis	Modulates the AMPK signaling pathway	[108]
Colon cancer	HT-29	Inhibits proliferation and induces apoptosis	Mitotic inhibition, DNA replication, and repair and growth factor signaling	[109]
Colon cancer	HCT116	Inhibits tumor growth	Regulation of Ephrin receptor pathway	[110]
Colon cancer	HCT116	Inhibits proliferation and tumor growth	Down-regulation of Wnt/ss-catenin signaling	[111]
Colon cancer	SW480	Inhibits colon cancer cell migration	Suppresses nuclear factor kappa B activity	[112]
Esophageal carcinoma	Eca-109	Inhibits proliferation and angiogenesis		[113]
Leukemia	Leukemic U937 and HL-60 cells	Induces apoptosis	Downregulation of PI3K/Akt family proteins	[114]
Gallblader cancer	Mz-ChA-1, QBC939 and GBC-SD	Induces apoptosis	C/EBP homologous protein (CHOP) upregulation, inositol-requiring enzyme 1 (IRE1)/PKR-like endoplasmic reticulum kinase (PERK) phosphorylations, and caspase-12 activation	[115]
Gallblader cancer	GBC-SD NOZ	Cell cycle arrest, induces apoptosis, inhibits tumor growth	Activation of p53 pathway	[116]
Gastric cancer	AGS	Induces apoptosis and inhibits proliferation	Activation of caspase-3, caspase-8, and caspase-9, as well as regulation of Bcl-2 and Bax expression	[117]
Gastric cancer	SGC-7901	Induces apoptosis	Regulates SP1 and HSF1 expressions	[118]
Gastric cancer	AGS	Inhibits growth and survival of AGS cells	Blocks Transient receptor potential melastatin 7 channel activity	[119]
Glioblastoma cancer	U87MG	Induces apoptosis	MEK signaling pathway and reactive oxygen species	[120]
Glioma cancer	U87	Induces senescence-like growth arrest	Regulation Akt and p53/p21-dependent signaling pathways	[121]
Lung adenocarcinoma	A549	Induces apoptosis, inhibits proliferation and tumor growth	Downregulation of epidermal growth factor receptor	[122]

Table 1 (continued)

Tumor type	Cell lines	Antitumor activity	Mechanism	References
Lung adenocar-cinoma	HepG2, SK-Hep1, Huh-7, and Hep3B	Induces cell death	Upregulates DR5 expression, which is mediated by C/EBP homology protein (CHOP), an important endoplasmic reticulum stress responsive protein	[123]
Lung cancer	A549	Induces apoptosis	Inhibits PI3K-AKt signaling pathway	[124]
Lung cancer	Lewis lung carcinoma (LLC) cells	Induces apoptosis	Regulation of reactive oxygen species	[25]
Lung cancer	NSCLC A549, H1299, H358	Inhibits tumor invasion	Downregulation of Fucosyltransferase IV (FUT4)	[50]
Hepatocellular carcinoma	Hep1-6 Hep G2	Induces apoptosis, and inhibits tumor growth	Expression alterations of Bcl-2 family proteins	[43]
Hepatocellular carcinoma	SMMC-7721 Hep G2	Induces apoptosis, and inhibits tumor growth	The upregulation of caspase-3 and bax and down-regulation of Bcl-2	[125]
Hepatocellular carcinoma	HepB3	Induces apoptosis	Regulation of mitochondrial signaling pathways	[126]
Melanoma	A375	Inhibits proliferation and tumor growth	Inactivation of EGFR/MAPK pathway	[127]
Melanoma	U266 and RPMI8226	Induces apoptosis	Activation of Bcl-2-associated X protein	[128]
Melanoma	A375P, A375M, C8161, Mevo and SK-MEL-28	Promotes cell death	Inhibits NF-κB/p65 signaling pathway	[129]
Melanoma	A375 C8161	Inhibits proliferation	Down-regulation of histone deacetylase 3 (HDAC3) and increase of p53 acetylation	[130]
Melanoma	U266, RPMI8226 and SKO-007	Inhibits prolifera-tion	Secretion of IGF-1 and inactivation of the Akt/mTOR pathway	[131]
Melanoma	B16	Induces apoptosis, regulates cell cycle, and blocks angiogenesis in addition to inhibiting proliferation	Regulation of caspase-3 and bcl-2 expression	[132]
Melanoma	B16F10	Anti-metastasis	MMP-13 regulation	[133]
Ovarian cancer	HO-8910	Induces apoptosis	Downregulation of PI3K/Akt and XIAP pathways	[134]
Ovarian cancer	SKOV-3	Inhibits migration and invasion of ovarian cancer	Upregulation of autophagy-associated molecules including LC3 II, ATG5 and ATG7	[36]
Pancreatic can-cer	PANC-1 and SW1990	Inhibits vasculogenic mimicry	Downregulation of VE-cadherin/EphA2/MMP9/MMP2 expression	[135]
Prostatic cancer	PC-3 M	Inhibits migration	Inhibits aquaporin 1 expression	[75]

injury (ALI) by decreasing the levels of pro-inflammatory mediators and increasing the production of anti-inflammatory cytokines via Mer tyrosine kinase (MerTK)-dependent activation of the via phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway [18]. Ginsenoside Rg3 may also improve anti-inflammatory capacity by affecting PI3K/AKT/mTOR signaling pathway through Toll-like receptor 4 (TLR4), which is a potential target of ginsenoside Rg3 (Fig. 1) [19]. The anti-inflammatory role of ginsenoside Rg3 may be associated with its structure, a steroid glycoside. Steroid-like anti-inflammatory activity has also been widely reported [20, 21]. Steroid drug has been widely used in cases of inflammatory disorders by suppressing proinflammatory cytokines IL-1, IL-2, IL-6, IL-8, IFN-γ and TNF-α [22]. These findings provide a new view of the specific anti-inflammatory mechanism of ginsenoside Rg3.

Ginsenoside Rg3 increases antioxidant properties

Contingent upon concentration, reactive oxygen species (ROS) influence cancer evolution and can initiate or stimulate tumorigenesis [23]. Antioxidants are regarded to play an important role to control ROS levels. Free radicals commonly cause oxidative damage which is a vital factor of formation, and development of cancers. Antioxidants

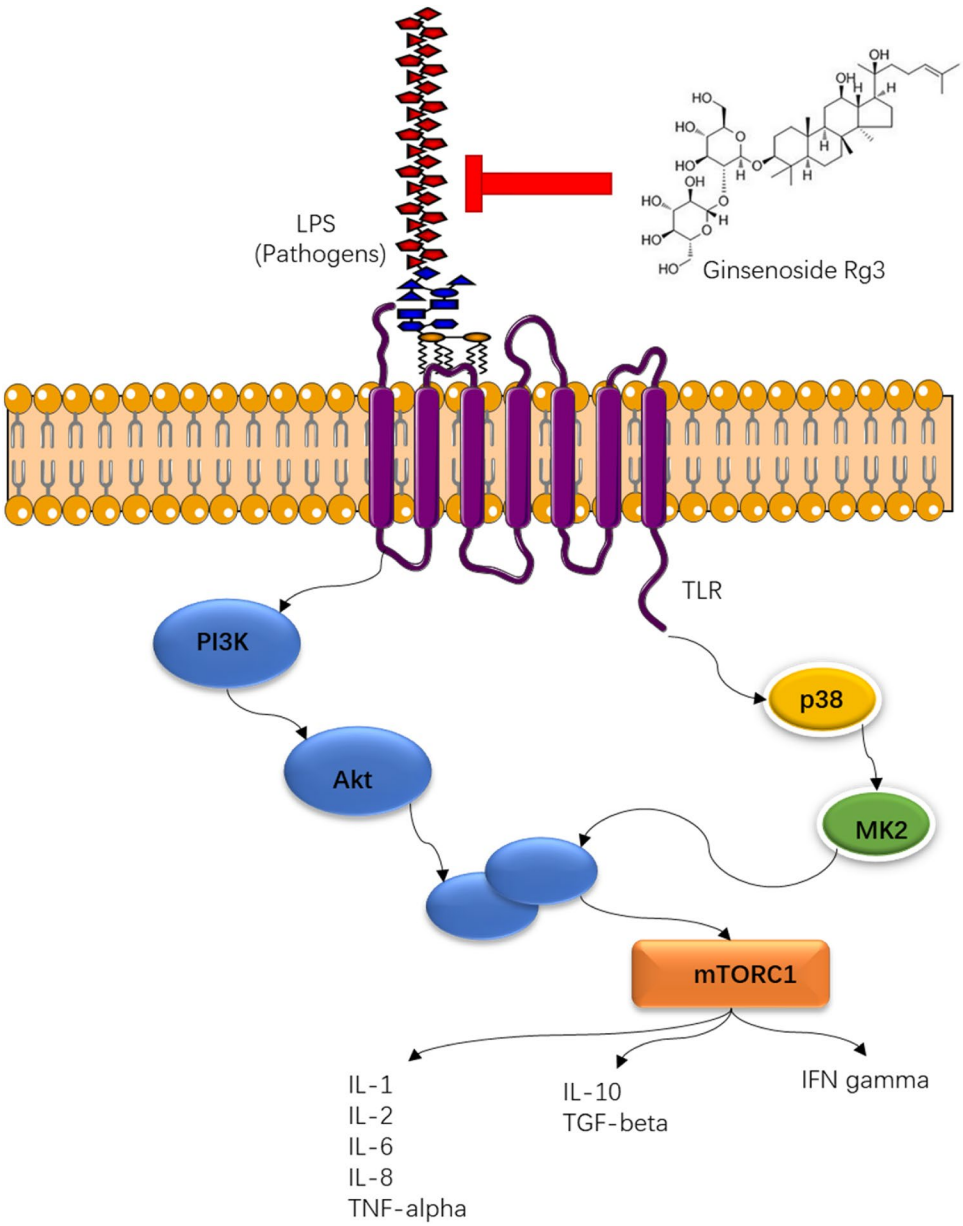

Fig. 1 Ginsenoside Rg3 suppresses inflammation in tumor cells via phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway. Diverse pathogens may activate PI3K/Akt/mTOR signaling pathway via their LPS binding Toll-like receptor (TLR) ligands. mTORC1 stimulation promotes the expression of anti-inflammatory. These activities may be regulated by ginsenoside Rg3, which can inhibit LPS binding TLR

belong to natural and synthetic origin have been tested in clinical trials against oxidative stress, and may be beneficial in cancer control [24]. Ginsenoside Rg3 having antioxidant potential is used in the treatment of cancers by regulating ROS levels [25], which include oxygen ions/$O_2^{\cdot}$, free radicals (superoxide/O_2^- and hydroxyl radicals/·OH) and peroxides (hydrogen peroxide/H_2O_2) in tumor cells [26, 27]. Ginsenoside Rg3 plays an important role in antioxidant activities, and is known to exert antioxidant effects by increasing the activity of antioxidant enzymes and related biomolecules, which can scavenge free radicals [28]. Ginsenoside Rg3 has been found to induce the activity of intracellular antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) (Fig. 2a) [29], which is involved in scavenging free radicals (Fig. 2b). The antioxidant ability of ginsenoside Rg3 may be due to its steroid structure since steroid drugs have been widely reported to have antioxidant activities [30].

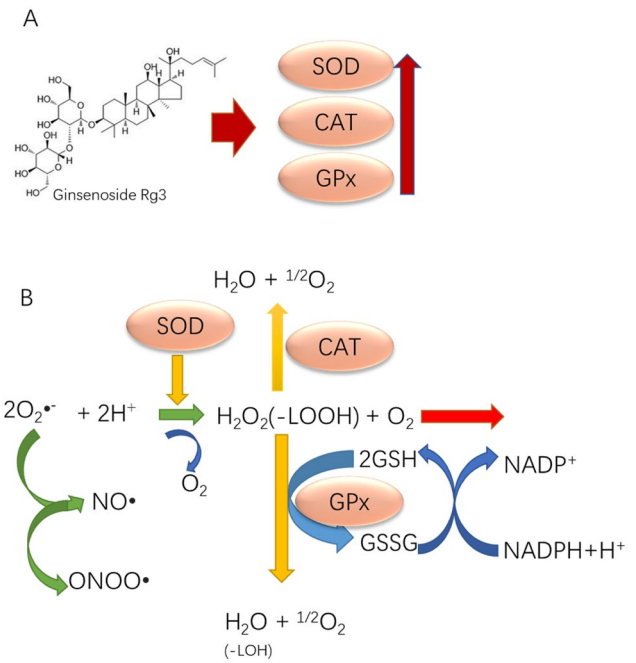

Fig. 2 The molecular mechanism for the antioxidant activity of Ginsenoside Rg3 by increasing the levels of antioxidant enzymes. A, ginsenoside induces the increase in the activity of antioxidant enzymes. B, antioxidant enzymes are involved in the transformation of ROS and their by-products into stable nontoxic molecules, which represents the most important defense mechanism against oxidative stress, which is produced by tumor cells

Ginsenoside Rg3 induces cancer cell apoptosis

Apoptosis induction is a potential approach and has been developed as the therapeutic methods for promoting the effective elimination of cancer cells [31]. The combination of ginsenoside Rg3 and 5-FU promotes the apoptosis of colon cancer cells in vitro by affecting PI3K/Akt signaling pathway [32]. Ginsenoside Rg3 stimulates cytotoxicity and apoptosis of Paclitaxel by preventing nuclear factor kappa B (NF-κB) signaling and regulating Bax/Bcl-2 expression on triple-negative breast cancer and should be regarded as a good chemosensitizing agent for cancer treatment [32].

Ginsenoside Rg3-based polypeptide nanoparticles is effective in the treatment of colon cancer by inducing cancer cell apoptosis [33]. The combination of oxaliplatin and ginsenoside Rg3 increased the anti-tumor effect and may inhibit the proliferation and promote the apoptosis of hepatocellular carcinoma via regulating the expression of proliferating cell nuclear antigen and cyclin D1 [34]. When ovarian cells were treated with ginsenoside Rg3, cell apoptosis was found to be induced while cell metastasis and invasion were also inhibited. Ginsenoside Rg3 inhibits cell proliferation and promotes apoptosis of ovarian cancer cells [35]. Ginsenoside Rg3 not only inhibits ovarian tumor cell proliferation and promotes its apoptosis, but also prevents tumor angiogenesis. Autophagy activity has also been found in ovarian cancer cells after ginsenoside Rg3 intervention [36].

One important cellular response to DNA damage is the induction of apoptosis to prevent daughter cells from inheriting mutations if the repair fails. Some findings demonstrated that ginsenoside Rg3 treatments induced DNA damage of non-small cell lung cancer cells (NSCLC) by affecting by activating vaccinia-related kinase 1 (VRK1)/phospho-53BP1 (P53BP1) pathway, which opens a new window for developing a new drug in the prevention of cancer progression [37]. Further work also showed that the ginsenoside Rg3 exhibits a significant anti-cancer effect on non-small cell lung cancer by inducing apoptosis via ROS/c-Jun NH2-terminal kinase (JNK)/p53 pathway [38] The tumor suppressor p53, a potent inducer of apoptosis, triggers autophagy by controlling several proteins, and plays a pivotal role in DNA damage-induced apoptosis [39]. Rg3 inhibited the Warburg effect in ovarian cancer cells via H19/miR-324-5p/pyruvate kinase M2 (PKM2) pathway, which is associated with various biological processes including metabolism, proliferation, apoptosis, migration and invasion of tumor cells [40].

Recent work showed that ginsenoside Rg3 inhibited the proliferation and migration of human osteosarcoma cells and stimulated apoptosis in a concentration-dependent

way. Ginsenoside Rg3 reduced the expression levels of Bcl2 and PI3K/AKT/mechanistic target of rapamycin (mTOR) but increased the levels of caspase3. Therefore, Ginsenoside Rg3 inhibits the proliferation of osteosarcoma cell line and induces their apoptosis by affecting apoptosis-related genes and PI3K/AKT/mTOR signaling pathway [41]. Erlotinib/Ginsenoside Rg3 treatment reduced the levels of p-epidermal growth factor receptor (EGFR), p-PI3K, and p-Akt. Ginsenoside Rg3 enhanced the efficacy of erlotinib to inhibit the proliferation of pancreatic cancer cells via induction of apoptosis and downregulation of the EGFR/ PI3Ks/AKT signaling [42].

Ginsenoside Rg3 inhibited prostate cancer cell growth via ROS-mediated cell cycle arrest [27]. Ginsenoside Rg3 improved erlotinib-induced apoptosis and increased the levels of caspase-3,9 and poly (ADP-ribose) polymerase (PARP). These results suggest that ginsenoside Rg3 may inhibit carcinoma growth via the regulation of ROS-mediated PI3K/AKT/mTOR pathway, which is involved with intrinsic apoptotic activity (Fig. 3) [43]. The apoptosis induced by ginsenoside Rg3 may be due to its steroid structure since steroid drugs have been widely reported to induce cancer cell apoptosis activity [44].

Immune regulation of ginsenoside Rg3

Both immunosuppressive and immunostimulatory are potential approaches in the cancer immunotherapy [45]. Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling mediates almost all immune regulatory processes, including those that are involved in tumor cell recognition and tumor-driven immune escape [46]. Ginsenoside Rg3 is stereospecific when stimulating the immune response, and more potent for treating cancers or other immune-mediated diseases [47]. Ginsenoside enhances the antitumor activity of Taxol on Lewis lung cancer by targeting various signaling pathways, including the interleukin-6/Jak2/STAT3 via partly just like some receptors (Fig. 4) [48, 49]. The epithelial-mesenchymal transition (EMT) is an important factor in lung cancer metastasis, and targeting EMT is a possible therapeutic strategy. Fucosyltransferase IV (FUT4) and its synthetic cancer sugar antigen Lewis Y (LeY) is often elevated in many cancers. Ginsenoside Rg3 inhibits EMT and invasion of lung cancer by down-regulating FUT4-mediated EGFR inactivation and blocking MAPK and NF-κB signal pathways [50].

Programmed death ligand 1 (PD-L1) as one the most important immune checkpoint has been verified to be

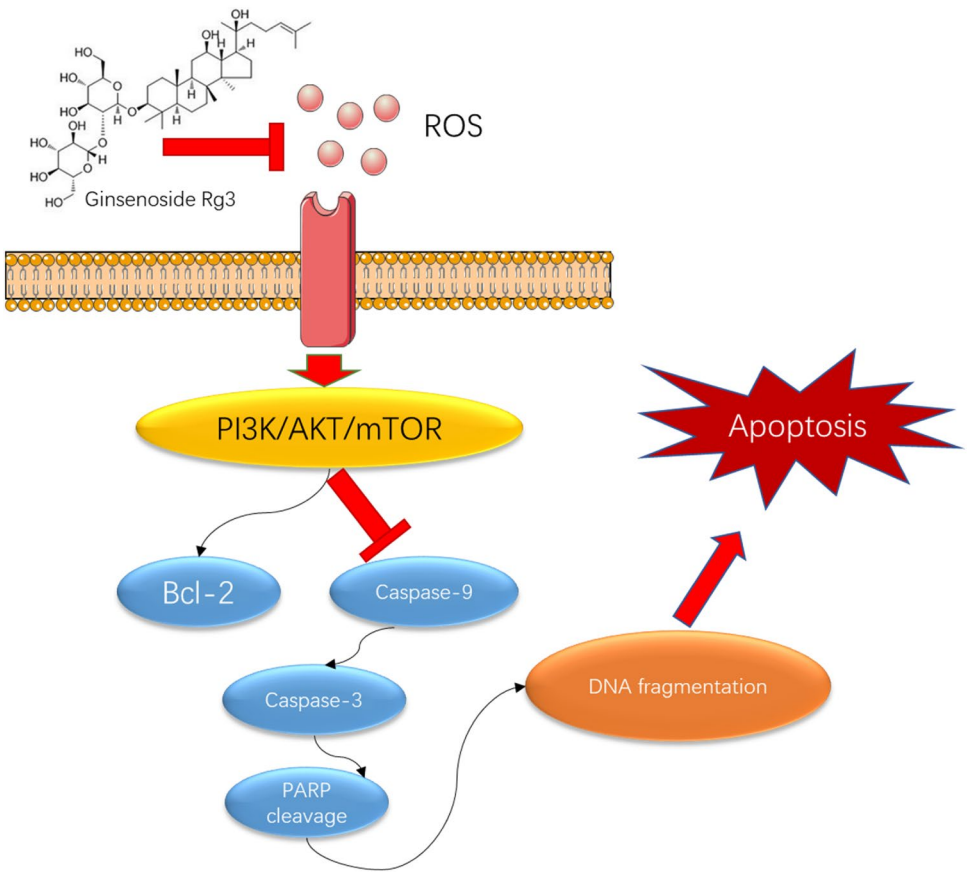

Fig. 3 Diagram showing the apoptosis induced by ginsenoside Rg3. Rg3 regulated ROS-mediated PI3K/AKT/mTOR, which is involved the apoptosis pathway and associated with the downregulation of Bcl-2 and upregulation of Caspase-3, Caspase-7, Cleaved PARP and Bax in tumor cells

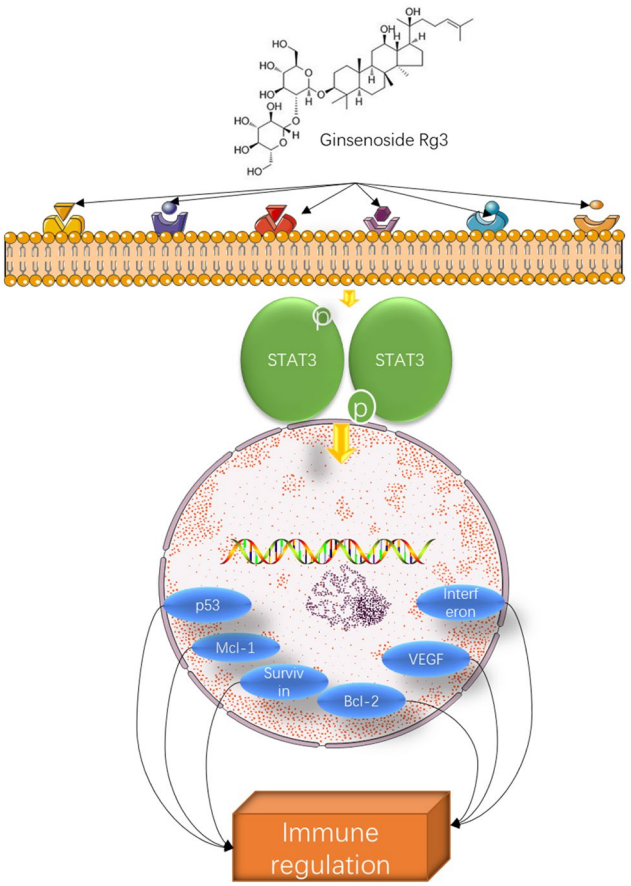

Fig. 4 A schematic presentation of JAK/STAT pathway regulated by ginsenoside Rg3 in cancer cells. JAK is closely related to cytoplasmic domains of many membrane receptors, which STAT3 regulate the expression of important proteins involved in immune regulation, including P53, interferon β, Fas and its ligand, and BAX

involved with chemotherapy resistance in NSCLC. Rg3 reduced NSCLC cell growth and alleviated its resistance to cisplatin. PD-L1 was overexpressed in a higher level in A549/DDP cells than A549 cells. Rg3 decreased the PD-L1 expression induced by chemoresistance and resumed the T cells cytotoxicity to cancer cells. NF-κB p65 and Akt are associated with PD-L1 expression and controlled by ginsenoside Rg3. Therefore, Rg3 is regarded as a new agent targeting PD-L1 in chemotherapy refractory NSCLC [51]. Ginsenoside Rg3, is commonly used to improve the immunocompetence of cancer patients undergoing chemotherapy. Ginsenoside Rg3 has protective effects on cyclophosphamide-induced immunosuppression, which is partially related to macrophages, T cells and Th1/Th2 balance. Rg3 can improve the reduced immunocompetence after cyclophosphamide injury [47]. The anticancer effect of Rg3 may be due to its downregulation of myeloid-derived suppressor cells (MDSC) and consequent repression of cancer stemness and EMT in breast cancer. Hence, we suggest the regulation of MDSCs through Rg3 treatment as an effective therapeutic strategy for breast cancer patients [6]. Ginsenoside Rg3 can effectively induce immunogenic cell death and may be useful in dendritic cell-based anti-tumor immunotherapy [52]. The immune responses regulated by ginsenoside Rg3 may be due to its steroid structure since steroid drugs have been widely reported to induce immune responses [53].

Ginsenoside Rg3 inhibits tumor angiogenesis

The critical role of angiogenesis has been widely reported in promoting tumor growth [54, 55] and metastasis [56, 57]. As tumor neovascularization is out of control, the tumor grows rapidly. Therefore, preventing tumor neovascularization can effectively inhibit tumor growth and metastasis.

VEGF [58, 59], fibroblast growth factor (FGF), angiogenin, platelet-derived growth factor (PGF), matrix metalloproteinase (MMP) etc., all these cytokines can contribute to promoting the formation of tumor blood vessels. This inhibition of angiogenesis caused by ginsenoside was associated with decreased protein and expression of VEGF, FGF and MMP [60]. Ginsenoside Rg3 has been reported to reduce VEGF expression in the patients with acute leukemia by inactivating PI3K/Akt and extracellular-signal-regulated kinase (ERK)1/2 pathways [61]. Some work showed that ginsenoside Rg3 treatment inhibited the expression of FGF in transplanted human lung squamous carcinoma in an animal model [62]. In stimulated macrophages, Rg3 was found to suppress matrix MMP-9 activity and suppress cyclooxygenase-2 (COX-2) expression [63]. Therefore, the angiogenesis biomarkers VEGF, FGF and MMP may be the main targets of ginsenoside Rg3 in the inhibition of tumor angiogenesis (Fig. 5).

Meta-analysis shows that ginsenoside Rg3 combined with chemotherapy may enhance short-term efficacy and overall survival, alleviate treatment-induced side effects, reduce VEGF expression, increase CD4/CD8 T cell ratio, and serve as a potential therapeutic strategy for NSCLC [64]. Rg3 exerts an inhibitory effect on the transforming growth factor (TGF)/Smad and extracellular signal regulated kinase signaling pathways in human keloid fibroblasts (KF). KF proliferation, migration, invasion and angiogenesis of KF can be greatly inhibited after ginsenoside Rg3 therapy. Furthermore, the results of a vivo assay showed that ginsenoside Rg3 prevented angiogenesis and attenuated collagen accumulation in keloids [65]. Rg3 also exhibited a suppressive effect on the MMP-9 gelatinolytic activity enhanced in the HaCat keratinocytes stimulated with TNF-alpha [66]. Ginsenoside Rg3 showing inhibitory functions on tumor angiogenesis may be due to its steroid structure since steroid drugs

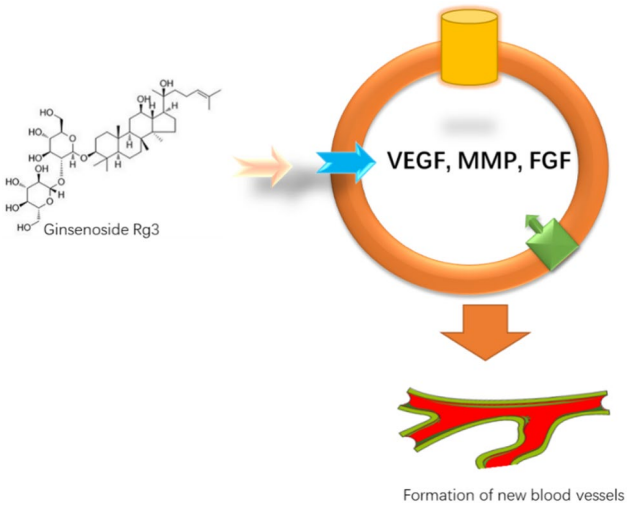

Fig. 5 The effects of ginsenoside Rg3 on the angiogenesis of tumor by targeting VEGF, MMP and FGF. Angiogenesis consists of the selection of some endothelial cells inside the capillary to begin angiogenic expansion. At its interior, a pro-angiogenic cell will carry VEGF, FGF and MPP etc.

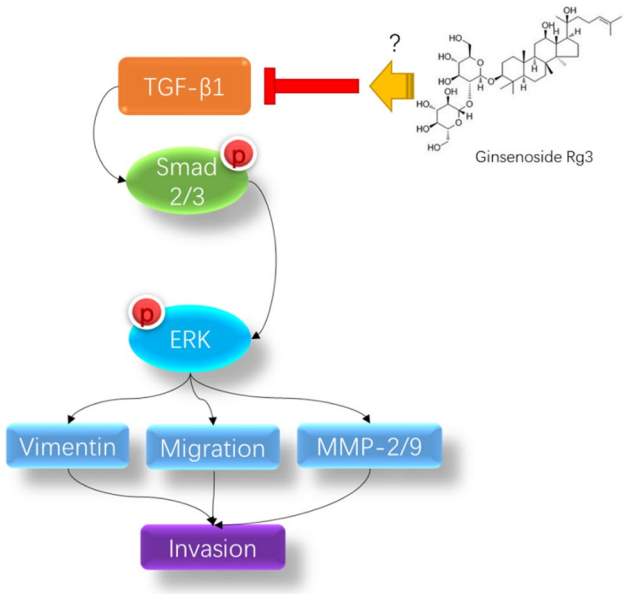

Fig. 6 Diagram depicting the inhibitory roles of ginsenoside Rg3 in the prevention of tumor metastasis via the inactivation of TGF-β1 / Smad signaling. ? Stands for the unknown process

have been widely reported to prevent tumor angiogenesis [67].

Rg3 reduces tumor metastasis

Tumor cell invasion and metastasis are closely associated with poor prognosis of cancer, which leads to cancer progression [68]. Ginsenoside Rg3 has been found to hinders cell growth, migration and invasion in human colorectal cancer (CRC) cells by downregulation of lncRNA colon cancer-associated transcript-1 (CCAT1) [69]. Rac-1/Cdc42 activity has been found to promote tumor cell invasion and metastasis [70]. Rg3 prevented thyroid cancer cell metastasis by destroying the association of actin cytoskeleton in lamellipodia by reducing the levels of Rac-1/Cdc42 in the cells. Rg3 showed good antitumor and anti-metastatic activities in vitro and in vivo, and has shown positive activities in antitumor [71]. Rho GTPase activating protein 9 (ARHGAP9), a member of RhoGAP family, has been identified to suppress the migration and invasion of hepatocellular carcinoma cells through up-regulating FOXJ2/E-cadherin [72]. Ginsenoside Rg3 hinders the metastasis and invasion of liver cancer cells by enhancing the protein levels of Rho GTPase activating protein 9 (ARHGAP9) [73]. Aquaporin 1 (AQP1) water channel participates in cancer cell proliferation, invasion, metastasis and angiogenesis, which may lead to tumor development [74]. Ginsenoside Rg3 has been reported to reduce the incidence of metastasis by inhibiting the expression of AQP1 in PC-3 M prostate cancer cells [75].

MMP-2 and MMP-9 expressions, and EMT is correlated with HCC metastasis and invasion [76]. Rg3 could inhibit migration and invasion of nasopharyngeal carcinoma (NPC) cells. This effect of Rg3 might be mediated through regulating MMP-2 and MMP-9 expressions and suppressing EMT [77]. EMT is a pivotal cellular process during which epithelial polarized cells become motile mesenchymal-appearing cells, which, in turn, cells transit between epithelial and mesenchymal states, and they play integral roles in normal tissue development and cancer metastasis [78]. TGF-β1 induces the EMT to promote tumor migration, invasion, and anoikis resistance [79]. Therefore, the inhibition of TGF-β1-induced EMT will be a potential approach to prevent tumor invasion and metastasis. Rg3 significantly decreases TGF-β1-regulated MMP-2 and activation of Smad2 and p38 MAPK (Fig. 6) [80]. Ginsenoside Rg3 showing inhibitory functions on tumor metastasis may be due to its steroid structure since steroid drugs have been widely reported to prevent tumor metastasis [81, 82].

Ginsenoside Rg3 reduces tumor chemoresistance and radioresistance

In various cancers, chemoresistance is a major hindrance for a cure [83, 84]. Therefore, it is necessary to explore a novel drug to reduce their chemoresistance. Recently, more and more researches have demonstrated that Ginsenoside Rg3 is involved in chemotherapy resistance in various types of cancers, making

it a promising Chinese herbal monomer for oncotherapy [85]. EGFR/PI3K/AKT signaling pathway is associated with the degrees of tumor chemoresistance [86]. Ginsenoside Rg3 improves the anti-proliferative action of erlotinib and reduces the chemoresistance of pancreatic cancer cells by inactivating the EGFR/PI3K/Akt signaling pathway [42]. Cetuximab and chemotherapy are often used for the initial treatment for CRC. However, the cure rate for CRC is still very low because of its chemoresistance. Ginsenoside Rg3 was found to reduce the chemoresistance of CRC by inhibiting the NF-κB signal [87].

Radiation therapy is an important way for various cancer therapy. However, most patients die of the tumor recurrence when the tumors produce resistant ability to radiotherapy. Recent work showed that ginsenoside Rg3 enhances the therapeutic results of radiotherapy for CRC by inhabiting NF-κB and NF-κB-mediated genes, resulting in the prevention of CRC development and prolongation of the lifespan of an animal model [88]. These results suggest that ginsenoside Rg3 is a potential drug to reduce tumor chemoresistance and radioresistance. Ginsenoside Rg3 increasing the tumor sensitivity to chemical therapy may be also due to its steroid structure since steroid drugs have been widely reported to reduce tumor chemoresistance [89].

The stereoselective effects of two epimers of Rg3

Rg3 has two stereoisomeric pairs, 20(S)-ginsenoside Rg3 [20(S)-Rg3] and 20(R)-ginsenoside Rg3 [20(R)-Rg3] with different pharmacological functions due to their different structures. Compared with 20(S)-Rg3, 20(R)-Rg3 shows higher anticancer activities for hepatocellular carcinoma study BY stimulating ConA-induced lymphocyte proliferation and increasing the levels of Th1-type cytokines interleukin-2 and interferon-γ [90]. Further work showed that 20(R)-Rg3 may have more potency and efficacy than 20(S)-Rg3 by preventing the migration and invasion of breast cancer cell line MDA-MB-231 [91]. However, different stereoisomer-specific anticancer activities have also been reported that 20(S)-Rg3 but not 20 (R)-Rg3 promotes cancer cell death in a dose-dependent manner by inducing the apoptosis of human liver cancer cell line HepG2 via the regulation of the levels of Bcl2 and Fas [92]. Much work is required to understand the differences caused by stereoisomer-specific anticancer activities of Rg3.

Rg3 metabolism and pharmacokinetics

The half-life of Rg3, absorption and tissue distribution will be critical properties for first-pass success of a candidate antitumor drug. Metabolism and pharmacokinetic studies are necessary to understand these important properties. A big concern about clinical indication of ginsenoides Rg3 in particular is its high metabolic rate of these molecules. Pharmacokinetics study shows that an average half-life of Rg3 is less than 20 min when the ginsenoside was intravenously dosed at 5 mg/kg in rat, and no Rg3 was detected in rat plasma if oral administration at 100 mg/kg [93]. Other metabolism data approve that Rg3 can be easily transformed to active ingredients by gut microbiota [94]. 20(S)-Rg3 was thought to be more predominant in the liver than kidney [95]. To avoid short half-life, Rg3 nanoparticles were injected into the mice tail vein. The concentrations of Rg3 nanoformulations in the liver, spleen and lung tissue were higher than the control group only with Rg3 monomer at the end of experiments [96]. Comparatively, human being is quite different from rats in the metabolism and pharmacokinetics of Rg3, can be detected in the plasma for 8 and up to 216 h after oral or intramuscular administration [97].

Clinical indication of Rg3

The trials of Rg3 in combination with chemotherapy have been reported to exert better therapeutic effects than chemotherapy alone and increase the life expectancy of NSCLC patients after cancer surgery. The mechanism may be associated the improvement of immune and anti-tumor activities [98]. Acquired resistance is the main factor for limiting the usage of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) in the prevention of lung cancer development. Rg3 helps to increase progression-free survival (PFS) and improve objective response rate (ORR) after EGFR-TKI treatment in NSCLC patients [99]. Transcatheter arterial chemoembolization (TACE) is a marginally invasive method in the therapy of various tumors. However, TACE shows the risks and side effects of both chemotherapy and embolization. The combination of TACE and Rg3 can increase overall survival rate when compared to those who only received TACE in HCC patients. Rg3 intervention inclines to attenuate adverse effects associated with TACE [100].

The differences between the present review and previous reviews

There are some review papers on the topic describing the anti-cancer properties of Rg3 and the differences are significant between the present review and previous reviews. Sun et al. summarized the main anticancer mechanisms, also including apoptosis, inhibition of cancer cell proliferation, metastasis and angiogenesis, and improvement of

immunity [101]. Nakhjavani et al. reviewed the main anti-cancer mechanisms of Rg3 but only for breast cancer [97]. However, the main anti-inflammatory properties related signaling pathways of Rg3 were neither included nor discussed in these analyses. Although antioxidant properties were mentioned in these reviews, the possible mechanisms were not explored either. In the present review, we find that Ginsenoside Rg3 improves anti-inflammatory capacity by affecting PI3K/AKT/mTOR pathway signaling pathway through TLR4. Ginsenoside Rg3 increases antioxidant properties by affecting the activities antioxidant enzymes (SOD, CAT, GPx, GR), which are involved in scavenging ROS molecules $O_2^{\cdot}$, O_2^{-}, ·OH and H_2O_2. Deciphering related signaling pathway will be beneficial to understand the complex molecular mechanisms of Rg3 action, and becomes the main topics in the present review. Comparatively, the previous reviews mainly focus on the potential molecular targets of Rg3.

Conclusion

Ginsenoside Rg3 has shown remarkable anti-tumor functions with few side effects both in vivo and vitro experiments, including lung, colon, breast and colorectal cancers. Furthermore, ginsenoside Rg3 improves the therapeutic results and efficacy of chemotherapy and radiotherapy. Ginsenoside Rg3 is a safe and effective anti-tumor Chinese medicine ingredient by affecting multiple antioxidant, anti-inflammatory, and immune signaling pathways, inhibiting tumor cell proliferation and neovascularization, promoting tumor cell apoptosis, and reversing tumor chemoresistance, etc.,. Ginsenoside Rg3 shows various inhibitory functions on many types of cancer may be also due to its steroid structure. There are still some limitations of ginsenoside Rg3 utilization: its functional molecular mechanisms remain widely unclear. A few clinical trials have been reported to treat cancers using Rg3, including NSCLC and HCC [97]. Furthermore, stereoselective inhibitory functions of Ginsenoside Rg3, Rg2, Rh2, Rh1 and Proropanaxadiol Epimers on Six UDP-glurono-syltransferases have been evaluated in human liver microsomes [102]. However, there is still lack of the related information on the clinical trials. Therefore, much work focusing on many clinical experiments is highly needed and the optimization of Rg3 usage will be worth for further investigating.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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