Ginseng as cancer therapeutics: recent advances in functional and mechanistic overview

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ARTICLE TYPE

Recent advances in ginseng as cancer therapeutics: a functional and mechanistic overview

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Cancer is one of the leading causes of death worldwide. Ginseng, a key ingredient in traditional Chinese medicine, shows great promise as a new treatment option. As listed by the U.S. National Institutes of Health as a complementary and alternative medicine, its anti-cancer functions are being increasingly recognized. This review covers the mechanisms of action of ginsenosides and their metabolites, which can modulate signaling pathways associated with inflammation, oxidative stress, angiogenesis, metastasis, and stem/progenitor-like properties of cancer cells. The emerging use of structurally modified ginsenosides and recent clinical studies on the use of ginseng either alone or in combination with other herbs or Western medicines which are exploited as novel therapeutic strategies will also be explored.

1 Introduction

Cancer is a major global public health problem, and there is an alarming increase in both its incidence and mortality rates in recent years. The World Health Organization (WHO) shows that in 2008, an estimated 12.7 million people were diagnosed with cancer and 7.8 million people died from cancer worldwide. It is anticipated that by 2030, an estimated 21 million new cases of cancer and 13.2 million cancer deaths will occur annually around the world.[1] Currently, chemotherapy is the mainstay of cancer treatment. However, chemotherapy has several disadvantages: (1) the development of chemoresistance is almost inevitable; (2) although these cytotoxic agents are effective against cancer, they are also toxic to normal cells causing serious side effects and complications (e.g. fatigue, pain, diarrhea, nausea, vomiting, and hair loss); and (3) such agents cannot be used for cancer prevention. Therefore, there is a great need for more effective cancer therapies.

Complementary and alternative medicines (CAM) have been rapidly growing in popularity in recent years. In the United States, approximately 40% of the population have used some form of CAM during the past 12 months.[2] Of the different kinds of CAM, ginseng is the most commonly used product because it is purported to have various beneficial effects, such as improving cardiovascular health[3], stimulating immune function,[4] increasing resistance to stress,[5,6] enhancing learning and memory,[7] and improving mental health and social functioning in normal adults.[8,9]

Ginseng use is also particularly popular among cancer patients, since multiple studies have associated the consumption of ginseng with cancer prevention and treatment, and with improved well-being during cancer therapy. Several case-control studies have shown that regular consumption of ginseng preparations could prevent cancers of the oral cavity, stomach, lung, liver, pancreas, ovary, and colon.[10,11] A 5-year cohort study of approximately 4,600 non-cancer individuals showed that consumption of ginseng significantly reduced the relative risk for cancer.[12] In a population-based epidemiological study of breast cancer, patients who had regularly used ginseng before cancer diagnosis and continued to use it after the diagnosis had significantly reduced risk of death and recurrence.[13] Ginseng use after cancer diagnosis was also found to correlate positively with the quality of life scores, particularly in the psychological and social well-being domains.[13] A recent randomized double-blind study also reported that daily consumption of 1,000-2,000 mg of American ginseng could help reduce cancer-related fatigue.[14] In fact, one of the earliest studies demonstrating the cancer preventive effects of ginseng in mice was a study published in 1983, in which oral administration of Korean red ginseng prevented the incidence and retarded the growth of lung cancer induced by urethane and aflatoxin B1.[15] Later, oral administration

of ginseng has also been shown to confer a protective effect against mammary gland cancer in rates injected with N-methyl-N-nitrosourea-injected rats.[16]

Over the past 30 years, great efforts have been made to identify the compounds in ginseng with anti-cancer activity, such as ginsenoside Rg3 and Rh2. Some of these compounds are now available as over-the-counter drugs in China and worldwide. The U.S. Food and Drug Administration (FDA) rates ginseng as GRAS (generally recognized as safe), and it is widely accepted as a CAM in cancer treatments in the U.S. and Europe. Globally, 80,000 tons of ginseng products are produced annually and the market is estimated to be worth over US$20 billion.[17] This review summarizes our current understanding of ginseng oncologic pharmacology and its anti-cancer actions. Recent evidence on the use of ginseng in cancer therapy and as an adjuvant treatment will also be discussed.

2 Ginseng

2.1 Brief History and Current status

"Ginseng" is translated from the Chinese words "人參" (Renshen) meaning "essence of men". Ginseng is traditionally used as a restorative medicine and conventionally refers to Asian ginseng. It has been the most widely used and acclaimed herb in Chinese communities for thousands of years. Detailed medical applications of ginseng were officially recorded in the "Compendium of Materia Medica (Bencao Gangmu 本草綱目)" in 1758, in which it was held in high esteem and crowned as the "King of All Herbs". Ginseng species were unknown in the Western world until the discovery of American ginseng in 1716 by the Jesuit priest Father Joseph Francois Lafitau near Montreal/Ottawa, Canada. In 1843, the Russian botanist Carl A. Meyer gave Asian ginseng the botanical name "Panax", which means "all-healing" in Greek. At least 9 species of ginseng have been classified under the Panax family, including *Panax quinquefolius* (American ginseng), *Panax notoginseng* (Sanqi 三七/Tian-qi 田七), *Panax japonicus* (Japanese ginseng), *Panax vietnamensis* (Vietnamese ginseng), and *Panax trifolius* (Dwarf ginseng). Siberian ginseng (*Eleutherococcus senticosus*) is also frequently found on the market. However, Siberian ginseng is only distantly related to the Panax family and can be considered to be an entirely different plant species.

2.2 Ginsenosides: major therapeutic constituents of ginseng

There are 3 key constituents of ginseng, namely saponins, polysaccharides, and phenolic compounds. The relative abundance of these constituents in ginseng are ~5% polysaccharides (with a total water soluble sugar content of 16.1-17.2%), ~3% saponins, and ~0.4% phenolic compounds as measured from a 4-yr-old Korean ginseng.[18] Ginseng polysaccharides are a diverse group of sugars that are composed of various types of glycosidic bonds (e.g. beta-1,3, beta-1,6 and 3,6-branching)[19] with molecular masses ranging from 1,200 – 260,000 Da.[20] The phenolic and flavonoid compounds are generally known to have antioxidant capacity.[21] Studies have indicated that the polysaccharide and phenolic/flavonoid fractions of ginseng also possess immuno-modulatory and anti-cancer activities.[22,23] However, their mechanisms of action are largely unknown. In 2011, a glycosylated protein called gintonin was newly identified in ginseng at a concentration of ~0.2% of crude extract.[24] Gintonin has attracted considerable attention and have been suggested to have anti-cancer activity via certain types of G-protein coupled receptors.[24,25] Among the constituents of ginseng, saponins have been extensively investigated pharmacologically and have been demonstrated to trigger physiological responses via steroid receptors. Saponins found in ginseng are generally known as ginsenosides. Approximately 100 ginsenosides have been identified since their first description in the 1960s by Shibata's group.[26] Some ginsenosides are found throughout the plant (e.g. Re, Rg1, Rh1),[27] whereas some are unique to specific structures, such as stems and leaves (e.g., Quinquenoside L10, L14 and L16),[28] fruits (e.g., 25-OH-PPD and 25-OH-PPT),[29] and flower buds (e.g., Floralginsenoside M, N, O, and P).[30] Many ginsenosides have been reported to have immunomodulatory and anti-cancer activities. Ginsenosides, but not the polysaccharides, can induce pro-apoptotic molecules and cell death in HCT116 colon cancer cells, although both can significantly inhibit their growth.[31] Gintonin mainly affects ion channel behavior and repeated treatments may cause cell desensitization,[32] whereas ginsenosides can target multiple receptors and enzymes without rapid loss of response via desensitization. Data from an unpublished study demonstrated that ginseng polysaccharides could stimulate RAW264.7 macrophage cells to produce tumor necrosis factor-α, but this was suppressed by cotreatment with ginsenosides.[33] Whether the different constituents interacted or counteracted one another is not known, and this is an important question that warrants further investigation. Saponins are constantly being produced and accumulated, and their levels are directly proportional to the age of the plant. Typically, the root saponin content reaches peak levels at around 6 years in cultivated ginseng, and at around 10 years for the wild ginseng.[34,35] These ginsenosides are mostly concentrated in the root (3-6% by weight).[34] Those first isolated from the root are named with a prefix "R", followed by a letter and numerical ranking of the chromatographic polarity in ascending order. For example, Ra is the least polar ginsenoside originating from the root, followed by Rb1, and Rg3 is more polar than Rg1.

The basic structure of ginsenosides consists of a steroidal core, with various sugar moieties (glucose (glu), rhamnose (rha), xylose (xyl), and arabinose (ara)) attached to the C-3, C-6, and C-20 positions (Fig. 1). Ginsenosides are grouped into two major categories based on the functional group on the C6 position. The panaxadiol group (PD) (e.g., Rb1, Rb2, Rc, Rd, Rg3, Rh2) contains a C6 hydroxyl group and the panaxatriol group (PT) (e.g., Re, Rf, Rg1, Rh1) contains a C6 sugar side-chain. Two minor classes of saponins include (a) the oleanolic acid group (e.g., Ro - C3: glu-glu and C28: glu) and (b) the ocotillol group (e.g., pseudoginsenoside F11- C6: glu-glu and C20/C24: epoxy). It is suggested that the biological activities of each ginsenoside are closely related to the type, position, and number of sugar moieties attached by the glycosidic bond at C-3 and C-6. Table 1 summarizes the structures and anti-cancer properties of exemplary ginsenosides. They will be further analysed in the following sections.

Each ginseng species has a unique ginsenoside profile. Taking Asian ginseng and American ginseng as examples, Asian ginseng exclusively contains ginsenoside Rf, whereas

ginsenoside F11 is exclusively found in American ginseng. Therefore, the Rf/F11 ratio can be used as a phytochemical marker to distinguish between American and Asian ginseng.[36] In addition, American ginseng contains higher levels of ginsenosides Rb1, Re and Rd, whereas Asian ginseng contains higher levels of ginsenosides Rg1, Rb2 and Rc, thus the Rb1/Rg1 ratio is another important biomarker to differentiate between these two ginsengs.[36] Such differences in ginsenoside profiles may correlate with specific physiological properties of the ginsengs. Thus, American ginseng is described as "cooling and soothing" to body conditions, whereas Asian varieties are thought to be "hot and stimulating".

Three heat-processed Korean ginsengs, red ginseng (steamed at 98-100°C for 2-3 h), Sun ginseng (steamed at 120°C for 2-3 h) and black ginseng (repeatedly steamed and dried 9 times) were found to have decreased contents of some common ginsenosides (Rb1, Rc, Rd, Re, and Rg1),[37] but contained an array of rare ginsenosides, including Rg5, Rk1, Rk2, Rk3, Rs4, Rs5, Rs6, and Rs7.[38-40] Such changes in ginsenoside composition give the heat-processed ginseng their signature anti-cancer properties. Among these 3 types of ginsengs, black ginseng had the highest amount of Rg3, whereas red ginseng contained the least Rg3, Rg5 and Rk1.[39,41,42]

Recently, heat processing (120°C for 3 h) of American ginsengs revealed elevated levels of the anti-cancer ginsenosides Rg3, Rg5 and Rk1.[43] Ginsenosides Rg3, Rg5, and Rk1 have been shown to be 50% more effective than cisplatin in inhibiting the growth of human hepatoma SK-Hep-1 cells.[44]

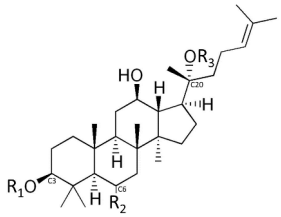

Fig. 1 The chemical structure of ginsenoside. R_1, R_2 and R_3 are the sites of sugar attachments on the steroidal skeleton of ginsenoside. Sugar moieties of selected ginsenoside are listed in Table 1.

2.3 Pharmacokinetics

Naturally occurring ginsenosides are bulky molecules that are poorly absorbed and rapidly degraded upon consumption. Indeed, pharmacokinetic studies in rats revealed that the oral bioavailability of ginsenosides Rb1 and Rg1 ranged from 0.1-4.35% and 1.9-18.4%, respectively, depending on administrative dosage and detection methods.[45-47] Most ginsenosides are chemically transformed by acid hydrolysis in the stomach,[48] followed by bacterial degradation in the gut, in which the sugar moieties are enzymatically cleaved in a stepwise manner.[49] Ginsenosides from the PT family are mainly degraded to Rh1 and protopanaxatriol (PPT), whereas those in the PD family are converted to active metabolite compound K.[50] These smaller metabolites are generally more bioavailable compared to the parent compounds.[51] For example, ginsenoside Rb1 can only be detected at very low levels in the plasma after oral administration that peak time is about 1 h,[47] whereas a significant amount of compound K was found in bacteria-associated animals that peak after about 8 h.[52,53] The fact that certain anticancer effects of orally administered ginseng extracts and ginsenosides *in vivo* cannot be reproduced in *in vitro* cultures further suggests that the effects of ginsenosides are mediated by their metabolites,[54] and a healthy intestinal flora is essential for the metabolism of ginseng to exert these effects. Once in the systemic circulation, ginsenosides can stay in the body for a considerable time. Ginsenosides Rb1 and Rg1 have been shown to decline with half-lives in beta phase of about 18 h and 14 h, and could still be traced in serum after 70 h and 24 h, respectively, of oral administration.[47] Structural analysis suggested that the pharmacokinetics of ginsenosides varied as the number of sugar moieties changed. Small ginsenoside metabolites PPD, PPT, compound K, and F2 have a serum half-life of 0.2-3.2 h, whereas the presence of 4 or more sugar moieties in ginsenosides Ra3, Rc, and Rd is found to significantly reduce the rate of elimination with a serum half-life of 7-25 h.[55] The stability kinetics of some ginsenosides *in vitro* has been studied. Ginsenosides Rb1, Rb2, and Rg1 are quite stable in the experimental condition of aqueous solution at 37°C and pH 7.0, whose degradation is almost negligible for 40 h.[56] The experiments described below were performed under these conditions to address the physiological relevance of the phenomena.

3 Anti-cancer activities

3.1 Inflammation, macrophages, and dendritic cells

The link between inflammation and the development of cancer was first proposed by Rudolph Virchow 150 years ago.[54] Since then, several studies have provided evidence to strengthen this link, and inflammation has two claims to notoriety. First, precancerous inflammation can cause increased genetic and epigenetic damage. Second, aberrant activation of oncogenes can cause inflammation. An inflammatory state is necessary to promote cancer progression and to achieve the full malignant phenotype, such as tissue remodelling, angiogenesis, metastasis, and suppression of the innate immune response.[57-59] Thus, efforts have been made to develop anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs, which have been reported to exhibit potent anti-cancer effects *in vitro* and *in vivo*.[60] Many plant-derived compounds, including ginsenosides, are known to have anti-cancer properties based on their anti-inflammatory effects, and their low toxicities render them excellent candidates for cancer therapy.

For example, ginseng total saponins could markedly reduce the production of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in lipopolysaccharide (LPS)-stimulated rat astrocyte and microglia cultures *in vitro*,[61,62] as well as in rodents receiving systemic administration of LPS.[61-63] These inflammatory mediators have been shown to induce the expression of various angiogenesis regulators, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), thereby enhancing vascular permeability,[64,65] and subsequently promoting tumor growth.[66,67] Several ginsenosides have been shown to have anti-inflammatory activities. For example, ginsenoside Rd down-regulated the expression of iNOS, COX-2 and NF-κB, and

Ginsenoside	Sugar moiety				Angiogenic?	Anti-cancer?	Receptor(s)	References
	NO.	R1 (C3)	R2 (C6)	R3 (C20)				
Protopanaxadiol-type								
Rb1	4	Glc-Glc	H	Glc-Glc	Anti	Yes	ERα/β	114, 133, 205
Rb2	4	Glc-Glc	H	Glc-Ara(p)	Anti	Yes	(n/a)	118, 119
Rc	4	Glc-Glc	H	Glc-Ara(f)	(anti)	Yes	(n/a)	207
Rd	3	Glc-Glc	H	Glc	(anti)	Yes	(n/a)	208, 209
Rg3	2	Glc-Glc	H	H	Anti	Yes	ER; PPARγ	95, 116, 118, 147, 210
Rh2	1	Glc	H	H	(anti)	Yes	GR	83, 211
Compound K (IH901)	1	H	H	Glc	Anti	Yes	GR	212-216
Panaxadiol	0	H	H	H	Anti	Yes	ERβ; GR	217-220
Protopanaxatriol-type								
Re	3	H	Glc-Rha	Glc	Pro	(n/a)	AR; ERα; GR; PR	143, 221, 222
Rf	2	H	Glc-Glc	H	(pro)	(n/a)	PPARα; Constitutive androstane receptor (CAR)	223, 224
Rg1	2	H	Glc	Glc	Pro	Yes	ER; GR	113, 225-228
Rh1	1	H	Glc	H	(pro)	Yes	ER	229, 230
F1	1	H	H	Glc	(pro)	Yes	(n/a)	231
Panaxatriol	0	H	H	H	Anti	Yes	ERβ; GR; PPARγ	217, 219, 232, 233

Table 1 Summary of structure and angiogenic properties of selected ginsenosides

suppressed the phosphorylation of ERK and JNK in rat paw challenged by carrageenan.[68] Ginsenoside Rh1 was found to be effective in suppressing IL-1β, iNOS, and COX-2 expression, and increasing IL-10 and hemeoygenase-1 expression in LPS or interferon (IFN)-γ-induced microglia.[70,71] IL-10 has been shown to not only elicit immunosuppressive effects, but also block VEGF and FGF2-induced neovascularization,[71] and reduce tumorigenicity of several cancer cell lines.[72,73] Topical application of ginsenoside Rg3 significantly suppressed epidermal ornithine decarboxylase activity, COX-2 expression, and skin tumor promotion in 12-O-tetradecanoylphorbol-13-acetate-induced mouse.[74] Similarly, application of its metabolite, compound K (IH-901) were found to reduce skin COX-2 and prostaglandin E2 expression.[75] Ginsenoside Rg1 showed significant anti-inflammatory activity in LPS-treated macrophages, and in acute and chronic inflammation models *in vivo*. These anti-inflammatory effects were glucocorticoid receptor (GR)-dependent, but lacked GR-associated side-effects, such as hyperglycemia and osteoporosis.[76] Dendritic cells are widely considered to be the major antigen-presenting cells in T cell immune responses.[77] Ginsenoside compound K and PPT have been shown to promote the differentiation of peripheral blood monocytes into dendritic cells, suggesting a potential use in cancer immunotherapy.[78] In LPS-challenged splenocyte culture and rat models, it was shown that Rp1, a synthetic ginsenoside, could suppress inflammatory responses by enhancing dendritic cell activation, thereby increasing regulatory T cell populations and anti-inflammatory cytokine IL-10 expression.[79]

3.2 Oxidative stress

Several lines of evidence indicate that cellular reactive oxygen species (ROS) levels play an important role in human carcinogenesis.[80,81] ROS increase DNA mutation and are a major cause of genome instability in cancer cells. In the tumor microenvironment, ROS produced by the rapidly growing cancer cells can induce oxidative stress in adjacent stromal fibroblasts, leading to the activation of angiogenic signaling and release of matrix metalloproteinases (MMPs) and cytokines, which promote immune tolerance and facilitate tumor growth. Superoxide dismutases (SODs) are important antioxidant enzymes responsible for the elimination of superoxide radicals.[82]

Ginseng is known to have anti-oxidative properties. Furthermore, ginsengs grown in mountainous forests have been shown to possess greater radical scavenging activity compared to cultivated ginseng.[83] In a cell free system, methanol extracts of both American ginseng and Asian ginseng could protect supercoiled DNA from peroxyl radical induced breakage.[84] Compared to Asian ginseng, American ginseng appeared to have a greater affinity for free radicals and was more capable in delaying lipid peroxidation, which could be attributed to the higher content of ginsenoside Rb1 in American ginseng.[84] Rb1 can react directly with hydroxyl radicals and hypochlorous acid, two of the strongest ROS, to protect plasmid DNA and prevent tyrosine chlorination.[85]

The intracellular anti-oxidative effects of individual ginsenosides were compared by subjecting fibroblasts pretreated with various ginsenosides to hydrogen peroxide.[86] The ROS scavenging activities of ginsenosides were ranked in the descending order: Rc>Rb2>Rg2>Rh2>Rh1>Rf>Rg3>Rg1>Rb1>Re>Rd.[86] Combinations of different ginsenosides have been shown to have synergistic effects. While ginsenoside Rb1 or Rg1 alone only mildly induced expression of Nrf2, which is a key transcriptional factor that binds to the antioxidant response element (ARE) and is critical for regulating the expression of many antioxidants and detoxifying enzymes,[87] coadministration

of Rb1 or Rg1 with PPT, a ginsenoside end-metabolite, synergistically activated ARE in liver cancer cells.[87]

Ginsenoside Re has been shown to protect cardiomyocytes from oxidative injury by scavenging hydrogen peroxide and hydroxyl radicals.[88] To enhance the antioxidative activities, ginsenoside Re can be modified by heat processing in the presence of alanine or lysine, which detaches the C20 sugar chain and to produce the less polar Rg2, Rg6, and F4.[89,90] The separated C20 sugar moiety then reacts with the alanine or lysine to generate Maillard reaction products (MRPs).[89,90] Compared to the naturally occurring ginsenoside Re, the resulting MRPs and ginsenosides Rg2, Rg6, and F4 had highly anti-oxidative activity and have greater anticancer effects via regulation of Bcl-2 and Bax and caspase-dependent apoptotic pathways.[89,90] Similarly, heating ginsenoside Rb2 in the presence of glycine can produce compounds with greater ROS scavenging activity.[91]

In mice, ginsenoside Rg3 has been shown to significantly inhibit cyclophosphamide-induced oxidative stress via the upregulation of catalase, SODs, and lysozyme activities, and the reduction of xanthine oxidase activity and levels of malondialdehyde and nitric oxide in multiple organs.[92]

3.3 Growth, death, and differentiation

Growth inhibition is a key theme in cancer therapy. Ginsenosides have been demonstrated to regulate core cell cycle regulatory machinery, including cyclin-dependent kinases (CDKs) and cyclins involved in G0/G1 progression. Ginsenoside Rf can induce G2/M cell cycle arrest and apoptosis in human osteosarcoma cells via the mitochondrial pathway.[93] Ginsenoside Rh2 has been shown to suppress cell growth in breast cancer,[94] prostate cancer,[95] leukemia[96] and pancreatic cancer.[97] Although both ginsenosides Rg3 and Rh2 could inhibit the growth of prostate cancer cells, the suppression was mediated via different signaling pathways, possibility due to the structural differences at the C3 position of Rg3 and Rh2.[95] Rg3 markedly activated JNK in androgen-independent PC3 cells, whereas Rh2 persistently activated p38 mitogen-activated protein kinases (MAPK) in androgen-dependent LNCaP cells.[95] Similarly, both Rg3 and Rh2 exhibited caspase-dependent and caspase-independent killing of colorectal cancer cells *in vitro*, but Rh2 was 3 times more potent than Rg3.[94] Most importantly, Rh2 did not cause any observable cytotoxicity to normal human colon epithelial cells even at the highest test concentration (60 μM).[98] Compound K, but not the parent ginsenoside Rb1, exhibited significant anti-proliferative and pro-apoptotic activity in colorectal cancer cells *in vitro* and *in vivo*.[99,100]

Telomerase activation has been observed in almost all tumors, but not in adjacent normal cells, suggesting that upregulation of telomerase may play an important role in carcinogenesis.[101] Korean red ginseng has been shown to induce apoptosis and inhibit telomerase activity in human leukemia cells.[102] Ginsenoside Rk1, often produced by heat-processing, and compound K, can inhibit telomerase activity in hepatocarcinoma and monocytic leukemia cells.[103,104] Ginsenoside Rh2 can induce differentiation in hepatocarcinoma,[105] leukemia[95,106] and melanoma cells,[107] partly by inhibiting telomerase activity.

The recent discovery of cancer stem cells (CSCs) has changed our view of carcinogenesis. The presence of CSCs has been demonstrated in various tumors. In contrast to other tumor cells, CSCs are drug resistant and display the ability to self-renew and differentiate. As such, it has been proposed that relapse after remission is likely due to the inability of standard chemotherapies to kill CSCs despite the effective elimination of the bulk tumor cells. Ginsenosides Rh1 and Rh2 can effectively induce agents which can trigger GR-mediated differentiation of pluripotent F9 teratocarcinoma cells to parietal endoderm-like cells.[108] Ginsenoside F2 has been shown to induce apoptosis in breast CSCs by activating the intrinsic apoptotic pathway and mitochondrial dysfunction, concomitant with autophagy progression.[109] These findings provide new insights into mechanisms underlying the anticancer activity of F2 and further detailed pharmacological studies could lead to novel therapeutic uses of F2.

3.4 Angiogenesis

Angiogenesis refers to the formation of new blood vessels from the existing vasculature. This tightly regulated process is integral to many physiological and pathological situations, including tumor growth. Angiogenesis is a multistep process involving endothelial cell growth, migration, and differentiation.[110] Many anti-angiogenic therapies have been developed to fight cancer and malignancies, and several compounds have been approved by the FDA, including the naturally occurring anti-angiogenic compound endostatin; VEGF antibodies (e.g. Bevacizumab, also known as Avastin®) that block its interaction with VEGF receptor; integrin $\alpha_v\beta_3$ antibodies (e.g. Vitaxin®) that function to induce apoptosis in the newly generated endothelial cells; and INF-α that suppresses the production of bFGF and VEGF, and MMP inhibitors (e.g. Marimistat® and Neovastat®) that prevent extracellular matrix (ECM) breakdown. However, these drugs often have undesirable side effects, such as hypertension, thrombosis, and skin toxicity,[111] and can only slow the growth of tumors but cannot completely eradicate the cancer.[112] For this, compounds that have both anti-angiogenic and anti-cancer properties but fewer side effects and will prove to be more useful.

3.4.1 Angiogenic factors

Ginsenosides from the PT family are generally pro-angiogenic, whereas those from the PD family are anti-angiogenic (Table 1). For example, ginsenoside Rg1, a member of the PT family, has been shown to promote blood vessel growth via the induction of hypoxia-independent VEGF expression.[113,114] On the contrary, ginsenoside Rg3, a member of the PD family, selectively suppressed VEGF expression,[115] and abolished VEGF and bFGF-induced endothelial sprouting.[116] Ginsenoside Rb1 has been shown to inhibit angiogenesis via induction of the anti-angiogenic modulator pigment epithelium-derived factor,[117] and Rb2 is found could suppress angiogenesis and metastasis *in vitro* and in tumor models *in vivo*.[118,119] Compound K was effective in reducing VEGF expression and disrupting bFGF-induced angiogenesis via regulation of p38 MAPK and Akt.[120] Hence, the anti-angiogenic ginsenosides from the PD family have been proposed as cancer treatments. This also suggests that American ginseng, which contains higher levels of PD ginsenosides, is pharmacologically more effective for these types of cancer treatments than Asian ginseng which contains higher levels of PT ginsenosides.

3.4.2 Endothelial progenitor cells

Endothelial progenitor cells (EPCs) have the ability to circulate, proliferate, and differentiate into mature endothelial cells, but do not have the characteristics of mature endothelial cells. It is noted that one-quarter of the cells of newly formed vessels have been shown to be EPC derived.[121] Besides their direct contribution to new vessels, EPCs secrete angiogenic growth factors, which could enhance the angiogenic process via paracrine signaling.[122] Therefore, targeting the bioactivity of EPCs could alter the angiogenic potency and influence the growth of early tumors.

Sun ginseng (200 μg/ml) has been shown to possess anti-senescent and anti-apoptotic effects in human-derived EPCs, indicating Sun ginseng could enhance EPC-mediated repair mechanisms and promote tumor angiogenesis.[39] Ginsenoside Rg1 and Rg3 are two saponins that possess opposing angiogenic properties. While Rg1 enhanced proliferation of bone marrow stromal cells/non-hematopoietic progenitor cells[123] and increased migration and proliferation of EPCs,[124] Rg3 is found to inhibit EPC differentiation by decreasing a distinct population of colony-forming EPCs in primary human umbilical cord blood.[125] Rg3 also attenuates VEGF-dependent Akt/endothelial NOS (eNOS), p38 MAPK, and extracellular signal-regulated kinases (ERK)1/2 signaling, inhibiting EPC migration and tube formation.[125,126]

3.5 Matrix remodelling and metastasis

Cell migration and invasion are crucial aspects of metastasis for the dissemination of cancer cells from an original site to other organs via the bloodstream or lymphatic system and for their subsequent colonization. Therefore, basement membrane integrity in part determines the metastatic potential of tumor cells. MMP-2 and -9, which can degrade collagen IV, the major ECM component of the basement membrane, have been suggested to be critical in this process.[127]

Ginsenosides have been reported to have an effect on several proteases involved in ECM degradation. For example, ginsenoside Rh2 suppressed pancreatic cancer cell migration by down-regulating the expression of MMP-2 and -9.[128] Ginsenoside Rb2 inhibited the invasion of uterine endometrial cancer cells via selective MMP-2 modulation.[129] Ginsenoside Rg3 inhibited tumor-induced angiogenesis and metastasis of highly invasive SKOV-3 ovarian cancer cells, which was attributed to the inhibition of MMP-2 and MMP-9 expression.[127,130] Ginsenoside Rd inhibited the migration of hepatocellular carcinoma cells by suppressing MMP-1, -2, and -7 expression via inactivation of ERK1/2 and p38 MAPK signaling and via activation of vinculin expression and focal adhesion formation.[131] Compound K was shown to inhibit MMP-9 expression in astroglioma by blocking MAPK signaling pathways.[132]

4 Mechanisms of action

4.1 Steroid receptor-dependent and -independent pathways

Ginsenosides are structurally described as triterpenoid saponins that contain a steroidal backbone. Although most naturally occurring ginsenosides have bulky sugar side chains that pose a huge steric hindrance for these molecules to bind to steroid receptors, various functional assays and molecular docking studies have provided evidence to show that ginsenosides can mediate their cellular activities by binding to the active sites of steroid receptors (Fig. 2). On the other hand, other studies suggest that ginsenosides may modulate their cellularactions via pathways independent of steroid receptors (Fig. 2). For example, ginsenoside Rb1 caused estrogen-receptor (ER)-specific transactivation which could be abolished by an ER nucleocytoplasmic shuttling inhibitor ICI 182,780, but it could not displace the endogenous ligand from the receptor, indicating that Rb1's estrogenic effects were independent of direct ER association.[133] Likewise, ginsenoside Rg1 induced both transcriptional and non-transcriptional activation of ER in endometrial Ishikawa cells *in vitro*, but treatment of Rg1 in sexually immature CD-1 or OVX B6 mice did not demonstrate typical estrogen-induced physiological changes, such as changes in uterine weight,[134] suggesting that a distinct estrogenic pathway may be involved. Rg1 has also been reported to act independently of direct binding to ER in breast cancer cells and such action is mediated via the activation of crosstalk between ER- and insulin growth factor receptor-I-dependent pathways.[135] Ginsenosides Re and Rc have been reported to induce c-fos expression in human breast cancer cells without interaction with glucocorticoid, androgen, estrogen, or retinoic acid receptor.[136] In the past, c-fos was believed to be an oncogene, whose increased expression was associated with the progression of breast cancer,[137] osteosarcoma[137] and endometrial carcinoma.[139] Recently, a murine liver cancer study showed that c-fos also possessed tumor suppressive and pro-apoptotic activities *in vivo*,[140] and loss of c-fos expression was associated with poor survival in patients with invasive epithelial ovarian cancer.[141] Therefore, the role of c-fos underlying ginsenoside Re and Rc activity could be context dependent, but this requires further investigation.

4.2 Genomic and non-genomic actions

Ginsenosides have been shown to mediate their cellular activities via both genomic and non-genomic pathways. For example, reporter gene assays revealed ginsenoside Rg1 could stimulate glucocorticoid receptor (GR) responsive elements and induce gene transcription in liver cells, indicating that it could mediate GR promoter stimulation[142] (Fig. 2). Gel shift assays revealed ginsenosides Rh1 and Rh2 could bind to glucocorticoid response element (GRE) binding proteins.[143] One intriguing aspect of ginsenosides are their non-genomic actions. For example, Rg1 has been shown to trigger the rapid non-genomic activation of PI3K/Akt via GR.[114,144] Likewise, ginsenoside Re, another functional ligand of GR, triggered rapid calcium ion influx (within minutes) in endothelial cells.[145] Rg3 could induce eNOS phosphorylation via the ER-mediated PI3K/Akt and AMP-activated protein kinase signaling pathways,[146] and caused rapid suppression of drug-induced Ca^{2+} influx.[147] Although the rapid non-genomic effects of ginsenosides have attracted increasing attention in recent years, the underlying mechanisms of action are still not clear. One possibility is through membrane-bound steroid receptors. However, the existence of functional steroid receptors associated with the plasma membrane is still under debate.[148] Alternatively, another hypothesis is through the cytosolic steroid receptors, which wound not only cause classic genomic but also rapid non-genomic effects resulting in the interaction of signaling processes, including PI3K/Akt.[149] Despite the unknown

underlying mechanisms, it is becoming increasingly evident that non-genomic interactions would be more beneficial for clinical use to maximize efficacy and minimize adverse effects or toxicity.[75]

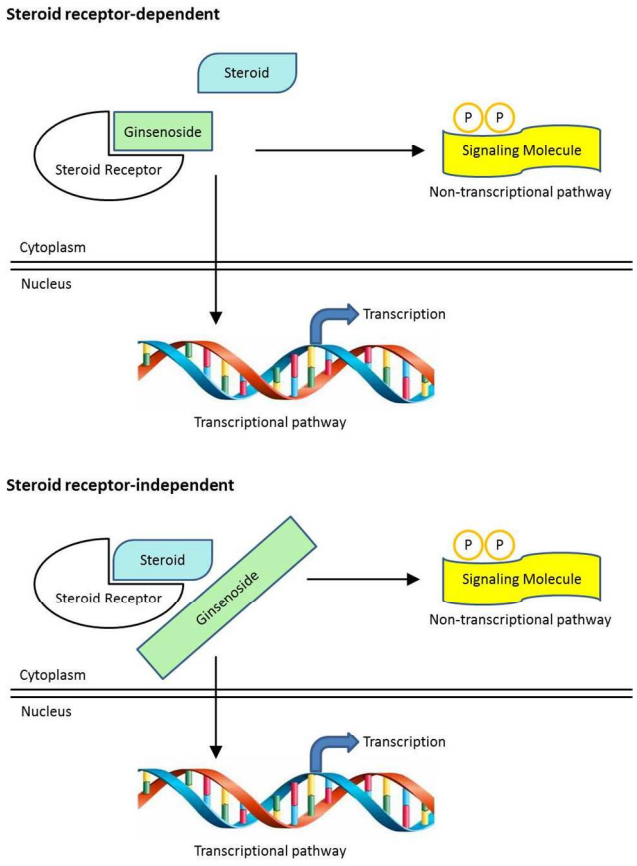

Fig. 2 Schematic of the proposed signaling pathways taken by ginsenosides. *Ex vivo* binding assays have shown that ginsenosides can compete with the native ligands for the ligand binding domain on steroid receptors. In turn, these ginsenoside-receptor complexes translocate into the nucleus to activate specific gene transcription and/or trigger cytoplasmic non-transcriptional responses. In some cases, ginsenosides initiate a receptor-dependent response but direct interaction between the ginsenosides and the ligand binding domain is not evident. Therefore, an unknown pathway may be involved.

4.3 microRNAs

Recent advances in cancer research have highlighted alterations in endogenous miRNA expression as one of the most important events of tumorigenesis in human cancers.[150] This class of small non-coding RNAs (~18-23 nucleotides) are responsible for an entirely new mechanism of gene regulation by directing mRNA degradation or by repressing post-transcriptional translation. Importantly, each miRNA can regulate the expression of multiple, functionally related genes, making miRNAs an exciting and promising new candidate for cancer intervention. Various ginsenosides have recently been demonstrated to modulate miRNAs, which has attracted great attention. For example, ginsenoside Rh2 has been shown to alter the expression of 24 miRNAs which may have roles in controlling angiogenesis, apoptosis, chromatin modification, cell proliferation, and differentiation in human non-small cell lung cancer cells.[151] Rh2 can regulate miRNA expression in glioma cells, possibly exerting its anti-proliferative role via miRNA-128.[152] Ginsenoside Rg3 can regulate the VEGF-induced angiogenic response via miRNA modulation.[153] Ginsenoside Rg1 has been shown to downregulate miR-214 and miR-15b expressions in human umbilical vein endothelial cells, resulting in increased eNOS and VEGFR-2 expression, respectively, which lead to *in vitro* cell migration and tube formation, and possibly promotes angiogenesis.[154,155]

5 Synthetic analogues of ginsenosides

Given their significant therapeutic importance and their relatively low abundance from the natural sources, attempts have been made to synthesize ginsenosides using biochemical approaches. Early approaches aimed at obtaining ginsenoside metabolites from ginseng extract, but the metabolites were absent or only present in extremely small quantities. One conventional method is to degrade the bulk ginsenosides by acid hydrolysis. However, this process is often accompanied by various side reactions, such as epimerization at C-20, or hydroxylation and cyclization of the side chain.[156] Other approaches were then developed, including soil bacterial hydrolysis,[157,158] enzymatic hydrolysis,[159] Smith degradation,[160] and alkaline hydrolysis,[161,162] but the yields from these methods were low. Later, "retro-synthesis" of ginsenosides has been used. Using ginsenoside Rh2 as an example, total ginsenosides are first completely hydrolysed under alkaline conditions to yield the metabolites PD and PT, which are then glycosylated at the C-3 position to generate the anti-cancer and anti-angiogenic Rh2.[163] A similar approach could be applied to generate the other ginsenoside metabolites.

In addition to the synthesis of both naturally occurring ginsenosides and their metabolites, structural modifications of ginsenosides have also been evaluated. Such modifications are aimed to enhance the biological activity while minimizing side effects, or increasing the systemic stability/availability of the ginsenosides. For instance, ginsenoside Rh2 can be converted to the dioctanoyl ester of Rh2 (D-Rh2) by reaction with octanoyl chloride. The resulting D-Rh2 is as effective as the parent compound in suppressing cancer growth, but exhibits significantly reduced cytotoxicity to other vital organs when compared to the parent compound (Fig. 3).[164]

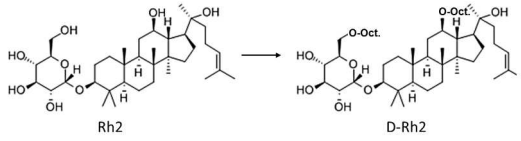

Fig. 3 Structural modification of ginsenoside Rh2 by reacting with octanoyl chloride. The structurally modified D-Rh2 has similar anti-cancer properties to the parent compound but shows reduced cytotoxicity (modified from Ref. 164).

Another example is a group of PT-derived polyacetylene small molecules. These ginsenoside analogues have promising cytoprotective activities and can mitigate cancer treatment-related undesirable side-effects, including body weight loss, lethality, neurotoxicity, and hematotoxicity in mouse xenograft model.[165] inflammatory activities and can induce cancer preventive Nrf2-dependent enzymes.[165] Hence, structurally modified ginsenosides

could be used as adjuvant treatments to reduce toxic side effects and pain during chemotherapy.

To enhance bioavailability, ginsenoside Rg3 was modified by conjugating with gold nanoparticles (AuNP) to improve its water solubility,[166] and ginsenoside Rg1, a compound that degrades by acid hydrolysis upon consumption, has been linked to polyethylene glycol (PEG). The resulting PEG-Rg1 is 2 times more stable than the parent compound in rat stomach,[167] and has 4 times higher hepatic selective uptake in mouse.[168] Ginsenosides Rg1 and Rb1 loaded on microparticles composed of an enteric-coating polymer and mucoadhesive polymer have enhanced oral bioavailability.[169] For Rh1, a metabolite of Rg1, reaction with octanoyl chloride forms Rh1-mono-fatty acid ester (ORh1).[170] ORh1 is less polar and thus has higher membrane permeability than its parent compound.[170] Similarly, compound K was converted to butyl ester (CK-B) or octyl ester (CK-O), which are 3-fold more bioavailable than the parent compound, are due to their more lipophilic structures.[171] Compound K has also been converted to the beta-cyclodextrin inclusion complexes (IH901-betaCD) that allows pH-dependent release. This complex has a 9-fold greater intestinal (pH 6.8) bioavailability and a 1.9-fold higher plasma concentration in rats compared to those given pure compound K powder.[172] The increased bioavailability and stability of these modified ginsenosides should greatly enhance their efficacies, particularly as cancer treatments.

In addition, based on the structure of ginsenosides Rg3 and Rg5, novel ginsenoside-derived compounds have been synthesized by modifying the double bond at the C20 position.[173] One of these ginsenoside-derived compounds, Rp1, was found to have greater anti-cancer and anti-angiogenic efficacy, and enhanced chemical stability compared to the parent compound.[174]

6 Therapeutic effects of ginseng in combination with other herbs or Western medicines

Several studies have evaluated the toxicity of ginsenosides in non-tumor cells or organs. Ginsenosides and ginseng extracts showed no observable toxicity in organs as measured by serum markers and did not significantly affect body weight.[175-177] In humans, no known side effects were observable at the recommended dose of 1-2 g of the crude ginseng or 200-600 mg of standardized extracts containing 4-7% ginsenosides.[178]

Indeed, ginseng has been observed to have several beneficial effects in patients with different types and stages of cancers. In a case-control study of 905 cancer patients, ginseng had a non-organ specific preventive effect even among individuals with minimal intake of ginseng (1-3 times a year).[10] In a randomized, placebo-controlled clinical study of 49 stage III gastric adenocarcinoma patients who had curative gastric resection and lymph node dissection, red ginseng powder capsule (4.5 g) or a placebo was prescribed daily in combination with their chemotherapy of 5-fluorouracil and cisplatin for six months after surgery. Patients taking ginseng had a significantly higher 5-year disease-free survival and overall 5-year survival, and had a stronger immunity.[179] In another randomized, double-blind study of 290 cancer patients, American ginseng (1,000-2,000 mg/day) was given daily for 8 weeks resulting in a significant reduction in cancer-related fatigue.[180]

There has been a growing interest in drug combinations, specifically combinations that have greater potency than individual drugs, or have reduced adverse side effects or complications. Drug combinations are also common in the practice of traditional Chinese medicine. “Fufang (複方)” tonics containing different combinations of herbs are often prescribed. This approach resembles the drug cocktail strategy used in the Western medicines. Among the top 10 most frequently prescribed Chinese herbal tonics for the treatment of cancer, 6 contain ginseng, and they are often combined with *Angelica sinensis* (dang qui 當歸).[181] Ginseng in combination with angelica root has been shown to exert synergistic anti-tumor effects in lung and breast cancer cells.[181,182] Zhu-xiang, a traditional Chinese herbal formula containing nine herbs including ginseng, has a significant pro-apoptotic effect in human breast cancer cells but minimal side effects in the normal human breast cells.[183] This formula has entered phase I clinical trials in Chang Chun.[183]

Recently, several studies have shown that ginsenosides are commonly used by cancer patients were able to enhance the therapeutic effects of conventional chemotherapeutic agents, and protecting normal tissues from chemotherapy-induced damage. For example, ginsenoside Rg3, known for its anti-cancer properties, synergistically act with a range of chemotherapeutic agents, including docetaxel, cisplatin, and doxorubicin, to suppress colon cancer cell growth by modulating apoptotic mediator expression.[184] The combined treatment of Rg3 with low-dose cyclophosphamide, gemcitabine, mitomycin C, tegafur or paclitaxel has been reported to significantly decrease tumor growth and angiogenesis, reduce tumor burden, and prolong the life of mice in ovarian and lung cancer models.[185-188] Cotreatment of Rg3 with low-doses of modified fluoropyrimidine carbamate (Capecitabine) was found to enhance anti-angiogenic activity in breast cancer.[189] This combination also exhibited less toxicity and reduced susceptibility to drug resistance.[189] Ginsenoside Rg3 combined with mitomycin C and tegafur (MF) in post-operative advanced gastric cancer patients resulted in decreased serum VEGF concentration and an improved survival rate.[190] In light of these encouraging data, a recent 4-year phase II clinical trial is ongoing in mainland China investigating the cotreatment of ginsenoside Rg3 (20 mg twice daily, po) with oxaliplatin (130 mg/m2 daily, i.v.) and capecitabine (1,000 mg/m^2, p.o.) in advanced gastric cancer patients.[191]

Besides Rg3, other ginsenosides such as Rh2 have been reported to have synergistic effects when combined with 5-FU by enhancing apoptosis in human breast cancer cells.[192] PPD, the end metabolite of Rg3, has been shown to enhance the anti-cancer activities of irinotecan and 5-FU in human colorectal cancer cells via the regulation of cell cycle transition and induction of apoptosis.[193,194] Cotreatments of PPD and the green tea catechin, epigallocatechin gallate, can act synergistically to cause cell cycle arrest and induces apoptosis in human colorectal cancer cells.[195]

The induction of drug-metabolizing enzymes (e.g. CYP3A4) and drug transporters (e.g. P-glycoprotein, P-gp) is one of the mechanisms underlying CAM-chemotherapeutic drugs, but this often leads to treatment failure because of low plasma levels of the chemotherapeutic drugs.[196] Ginsenosides Rg3, Rh2, compound K, PD and PT have been shown to suppress P-gp-

mediated multidrug resistance, thereby enhancing accumulation of chemotherapeutic drugs within the cancer cells and increasing the life span of mice.[197-199] However, in a recent study of 12 healthy individuals who took *Panax ginseng* for 28 days, CYP3A activity was induced but there was no change in P-gp function.[200] Zhang et al. showed that rats given *Panax ginseng* for 14 days had induced both intestinal and brain endothelium P-gp expression.[201] Differences in species, ginsenoside type, and ginseng preparations could account for differences in the results of these studies.

Negative interactions between Chinese herbal medicines and conventional chemotherapeutic drugs are often a concern. The first report of adverse interactions between ginseng and drugs with ginseng was published in 1987, which found that ginseng reduced the anti-depressant activity of phenelzine.[202] Since then, conflicting results on the interactions between ginseng and Western medications have been reported. In a randomized double-blind placebo-controlled study in healthy individuals, concurrent consumption of American ginseng preparation with warfarin was shown to reduce the effectiveness of this anti-coagulant.[203] However, in another two prospective randomized trials, coadministration of warfarin with *Panax ginseng* in ischemic stroke patients or with Korean red ginseng in patients with replacement cardiac valves did not cause any reduced effects.[204,205] So far, there is no conclusive evidence that ginseng preparations or ginsenosides impair the effects of conventional chemotherapeutic drugs.

7 Conclusion and future perspectives

In the light of the growing literature, ginseng holds great promise for future cancer treatments or as an adjuvant to cancer therapeutics in multiple cancer types. Ginsenosides exhibit diverse actions regulating most known modulators of carcinogenesis (Table 2). Because of various mechanisms of cell death employed by ginsenosides, it may be difficult for cancer cells to develop resistance to ginsenoside-induced cell death. Furthermore, the ability to kill tumor cells while causing relatively little toxicity to normal cells make ginsenosides attractive candidates for drug development. The different species, wild or cultivated, harvest time, and methods of processing could all impact the pharmacological effects, so it will be necessary in future studies to determine the influence of these variables. High-throughput expression arrays will prove useful to reveal the molecular functions of the different ginsenosides and how the different signaling networks are orchestrated. Further evaluations will also be needed to determine why ginsenosides have selective toxicity towards tumor cells and how this selectivity is achieved. Synthesized or modified natural ginsenosides are promising as cancer treatments, particularly if they can be made more bioavailable, efficacious, safe, and affordable. Combination therapy with conventional chemotherapeutic drugs has been proposed to be more effective. However, these therapies warrant further investigation using additional animal studies and large cohort clinical trials.

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Ginseng species	Experimental model	Effects	Signaling molecule(s) involved	Ref.
Asian ginseng	Rat primary mixed astrocytes	Anti-inflammatory	TNF-α, IL-1β, iNOS, COX-2	62
	Primary hippocampal neurons from chronic inflammation model of aged rats	Anti-inflammatory	IL-1β, IL-6	63
	[Cell free system]	Free radical scavenging, supercoil DNA protection		84
American ginseng	[Cell free system]	Free radical scavenging, supercoil DNA protection		84
	Cancer patients	Reduce cancer-related fatigue		180
Korean Red ginseng	BV2 murine microglial cells, B35 neuroblastoma cells, and rat primary microglial cells	Anti-inflammatory	iNOS, NFκB, MAPK, ILs	61
	U937 human leukemia cells	Anti-proliferation, apoptosis, inhibit telomerase activities	Bcl-2, Bcl-XL, caspase 3, COX-2, iNOS	102
	Stage III gastric cancer patients	Improve postoperative survival		179
Korean Sun ginseng	Human endothelial progenitor cells	Inhibits senescence-associated apoptosis		41
Protopanaxadiol-type				
Rb1	[Cell free system]	Free radical scavenging, plasmid DNA protection		85
	HepG2-C8 human hepatoma cells	Anti-oxidant	Nrf2-ARE	87
	HUVEC human endothelial cells	Anti-angiogenesis	PEDF	117

Ginseng species	Experimental model	Effects	Signaling molecule(s) involved	Ref.
Protopanaxadiol-type (Cont')				
Rb2	V79-4 Chinese hamster lung fibroblast cells	Anti-oxidant	ROS	86
	[Cell free system]	Modified ginsenoside - Anti-oxidant		91
	B16-BL6 mouse melanoma cells, 26-M3.1 colon carcinoma cells in syngeneic mice	Anti-metastasis, anti-angiogenesis	Fibronectin (FN) and laminin (LM)	118
	Rat lung endothelial (RLE) cells, B16-BL6 mouse melanoma cells	Anti-proliferation, anti-angiogenesis		119
	Ishikawa, HHUA, HEC-1-A human endometrial cancer cell	Inhibit invasion	MMP-2	129
Rc	V79-4 Chinese hamster lung fibroblast cells	Anti-oxidant	ROS	86
Rd	Rat *in vivo*	Anti-inflammatory	iNOS, COX-2, NF-κB, ERK, JNK	68
	HepG2 human hepatocellular carcinoma cells	Inhibit migration and invasion	MMP-1/2/7, p38 MAPK, ERK	131
Rg3	MCF-10A human breast epithelial cells and mouse skin	Anti-inflammatory	ODC, COX-2, NFκB	74
	Mice *in vivo*	Anti-oxidant	Catalase, SOD, lysozyme	92
	LNCaP, PC3 Prostate cancer cells	Cell detachment, anti-proliferation	MAPK	95
	Eca-109, 786-0 human esophageal carcinoma cells	Anti-angiogenesis	HIF-1α, COX-2, NFκB, STAT3, ERK1/2	115
	HUVEC human endothelial cells	Anti-angiogenesis	VEGF	116
	B16-BL6 mouse melanoma cells, 26-M3.1 colon carcinoma cells in syngeneic mice	Anti-metastasis, anti-angiogenesis	FN and LM	117
	Human endothelial progenitor cells	Inhibit differentiation	VEGF, Akt, eNOS	125
	Human endothelial progenitor cells	Inhibitor mobilization	VEGF, p38/ERK	126
	SKOV-3 human ovarian cancer cells	Inhibit metastasis	MMP-2, MMP-9	130
	HUVEC human endothelial cells	Anti-angiogenesis	miR-520h, EphB2/B4	155
	SW620 and HCT116 human colon cancer cells	Synergistic apoptotic and anti-proliferative effects with conventional chemotherapeutics	Bcl-2, IAP-1, XIAP, COX2, c-Fos, c-Jun, cyclin D1	183
	SKOV-3 human ovarian cancer cell transplanted mice	Synergistic anti-tumor effects with CTX and improve life quality		184
	Murine Lewis lung carcinoma transplanted mice	Synergistic anti-tumor effects with gemcitabine and improve life quality		185
	A549 human lung cancer cell transplanted mice	Synergistic anti-tumor effects with CPA and improved survival time		186
	MCF-7 human breast cancer transplanted mice	Synergistic anti-tumor effects with paclitaxel		188
	Advanced gastric cancer patients	Reduce serum VEGF level and enhance survival rate		189
Rh2	MCF-7, MDA-MB-231 human breast cancer cells	Cell cycle arrest	CDKs, cyclins, phosphorylated retinoblastoma protein (pRb), E2F1	94
	LNCaP, PC3 human prostate cancer cells	Cell detachment, anti-proliferation	MAPK	95
	HL-60, U937 human leukemia cells	Anti-proliferation	CDKs, cyclins, CKIs	96
	HL-60 human leukemia cells	Differentiation	Transforming growth factor-β (TGF-β)	96
	HCT116, SW480 huamn colorectal cancer cells	Apoptosis and paraptosis	Caspases, ROS	98
	SMMC-7721 human hepatocarcinoma cells	Differentiation, cell cycle arrest, inhibit telomerase activities	CKIs, cyclins	105
	HL-60 human leukemia cells	Differentiation, cell cycle arrest	Ca^{2+}/phospholipid-dependent PKC	100
	B16 mouse melanoma cells	Differentiation, cell cycle arrest	Melanin	107

Ginseng species	Experimental model	Effects	Signaling molecule(s) involved	Ref.
Protopanaxadiol-type (Cont')				
Rh2 (Cont')	F9 mouse teratocarcinoma cells	Differentiation	LM B1 and type IV collagen	108
	Bxpc-3 human pancreatic cancer cells	Inhibit proliferation, migration and invasion; induce apoptosis	MMP-2 and -9, caspase-3, -8 and -9, Bax Bcl-2 survivin and cyclin D1	128
	A549 human non-small cell lung cancer cells	Anti-proliferation	miRNAs	152
	U251, T98MG, A172 human glioma cells	Anti-proliferation	miR-128	153
Compound K (IH901)	Mouse skin *in vivo*	Anti-inflammatory	NFκB, ERK1/2, Akt, COX-2	75
	Human peripheral monocytes	Differentiation		77
	HCT116, SW480 huamn colorectal cancer cells	Cell cycle arrest, apoptosis	Caspases	99
	Nude mice - colorectal cancer xenograft tumor model	Cell cycle arrest	ATM/p53-p21 and FoxO3a-p27/p15 pathways, TGF-β, Rb	100
	HUVEC human endothelial cells	Anti-angiogenesis	p38 MAPK , AKT, VEGF	119
	U87MG and U373MG human astroglioma cells	Inhibit invasion	p38 MAPK, ERK, JNK,MMP9	132
F2	Breast cancer stem cells	Apoptosis, mitochondria dysfunction, autophagy	GFP-LC3-II and Atg-7	109
Protopanaxatriol-type				
Re	Primary chick embryonic ventricular myocytes	Anti-oxidant		88
	Primary chick embryonic ventricular myocytes	Modified ginsenoside - Anti-oxidant		89,90
Rg1	RAW264.7 murine macrophage, A549 human lung cells, MC3T3 mouse osteoblast precursor cells and mouse arthritis model	Anti-inflammatory	NFκB, IκB, MAPK	76
	HepG2-C8 human hepatoma cells	Anti-oxidant	Nrf2-ARE	87
	HUVEC human endothelial cells	Angiogenesis	PI3K/Akt, β-catenin/T-cell factor, VEGF	113
	HUVEC human endothelial cells	Angiogenesis	HIF-1α, p70S6K	115
	Rat bone marrow stromal cells	Proliferation		123
	Human endothelial progenitor cells	Proliferation, migration	VEGF	124
	HUVEC human endothelial cells	Angiogenesis	miR-214, eNOS	154
	HUVEC human endothelial cells	Angiogenesis	miR-15b, VEGFR2	155
Rh1	F9 mouse teratocarcinoma cells	Differentiation	LM B1 and type IV collagen	108
Panaxatriol	Human peripheral monocytes	Differentiation		77
	HepG2-C8 human hepatoma cells	Anti-oxidant	Nrf2-ARE	87

Table 2 Summary of preclinical and clinical studies ginsenoside's [20] anti-cancer effects

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