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REVIEW ARTICLE

Recent Advances in Ginsenosides as Potential Therapeutics Against Breast Cancer

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Abstract: The dried root of ginseng (*Panax ginseng* C. A. Meyer or *Panax quinquefolius* L.) is a traditional Chinese medicine widely used to manage cancer symptoms and chemotherapy side effects in Asia. The anti-cancer efficacy of ginseng is attributed mainly to the presence of saponins, which are commonly known as ginsenosides. Ginsenosides were first identified as key active ingredients in *Panax ginseng* and subsequently found in *Panax quinquefolius,* both of the same genus. To review the recent advances on anti-cancer effects of ginsenosides against breast cancer, we conducted a literature study of scientific articles published from 2010 through 2018 to date by searching the major databases including Pubmed, SciFinder, Science Direct, Springer, Google Scholar, and CNKI**.** A total of 50 articles authored in either English or Chinese related to the anti-breast cancer activity of ginsenosides have been reviewed, and the *in vitro*, *in vivo*, and clinical studies on ginsenosides are summarized. This review focuses on how ginsenosides exert their anti-breast cancer activities through various mechanisms of action such as modulation of cell growth, modulation of the cell cycle, modulation of cell death, inhibition of angiogenesis, inhibition of metastasis, inhibition of multidrug resistance, and cancer immunemodulation. In summary, recent advances in the evaluation of ginsenosides as therapeutic agents against breast cancer support further pre-clinical and clinical studies to treat primary and metastatic breast tumors.

Keywords: *Panax ginseng*, *Panax quinquefolius*, *Panax notoginseng*, Ginsenosides, Breast Cancer, Mechanism.

1. INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in females, responsible for 30% of newly diagnosed cancers, following by lung (13%) and colorectal (7%) cancers [1]. The risk of an American woman developing breast cancer over her lifetime is one in eight; while the risk for a man is one in 1000. It is estimated that about 263,694 new cases (including 2,550 male) and 40,041 deaths from breast cancer will occur in the United States in 2018 [1]. Although advances in chemotherapy and surgery have been made in the fight against breast cancer, researchers are still seeking a new cure for this disease.

Screening natural products or their derivatives for anticancer activity from traditionally used herbal medicine has become a hot research topic. Natural products are seen as a complement or alternative to chemotherapy not only to reduce the side effects but also to improve the efficacy of chemotherapy in cancer treatment [2]. The word panax in ginseng's botanical name means "all healing" or "cure all", so named because of the traditional belief that it contains numerous medicinal healing properties capable of treating all human ailments [3]. Ginseng has a proven safety record having been used in Asia for over two thousand years. There is increasing interest in exploring ginseng's anticancer properties, especially in combination therapy. It is, therefore, not surprising that ginseng attracted thousands of studies including its application in cancer, one of the most serious threats to human health.

The dry root of ginseng (*Panax ginseng* C. A. Meyer or *Panax quinquefolius* L.) is a widely used traditional Chinese medicine to manage cancer symptoms and chemotherapy side effects. *P. ginseng* (Asian ginseng) and *P. quinquefolius* (American ginseng) both belong to the same genus panax, family Araliaceae, and order Apiales. *P. ginseng* has been used as an herbal medicine for treating health-related problems in Asia for more than 2000 years [4]; while *P. quinquefolius* is native to the Appalachian Mountains in the United States and Canada and has been exported to Asia since the 18th century [5]. Today, ginseng is commercially grown in North America and Asia and remains one of the most widely used natural remedies for diseases and the best-selling medicinal herbs [6].

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The bioactive constituents of ginseng include ginsenosides, polysaccharides, polyynes, flavonoids, volatile oils, and fatty acids [7]. The efficacy of ginsenosides on the immune system, central nervous system, and endocrine system as anti-tumor, immune-boosting, anti-stress, and anti-neoplastic agents have been intensively reported [7-9]. The anti-cancer efficacy of ginseng is attributed mainly to the presence of ginsenosides, which have shown significant inhibitory activities against several types of cancer including breast, liver, lung, colon, and skin cancer *in vitro*, *in vivo*, and in some clinical trials [10-12].

To review the recent advances on anti-cancer effects of ginsenosides against breast cancer, we conducted a literature study of scientific articles published from 2010 through 2018 to date by searching the major databases including Pubmed, SciFinder, Science Direct, Springer, Google Scholar, and CNKI**.** A total of 50 articles authored in either English or Chinese related to the anti-breast cancer activity of ginsenosides have been reviewed. This review focuses on ginsenosides in Asian ginseng and American ginseng and summarized the *in vitro*, *in vivo*, and clinical studies on the anti-breast cancer activities of ginsenosides. The various mechanisms of action through which ginsenosides exert their anti-breast cancer activities are discussed, including modulation of cell growth and cell death, modulation of the cell cycle, inhibition of angiogenesis, inhibition of metastasis, inhibition of multidrug resistance, and cancer immune-modulation. In summary, recent advances in the evaluation of ginsenosides as therapeutic agents against breast cancer support further pre-clinical and clinical studies to treat primary and metastatic breast tumors.

This review provides useful information for future studies on ginsenosides derived from ginseng for the treatment of breast cancer. It should be noted that the current research on ginsenosides has encountered obstacles including multiple targets, complex mechanisms of action, and unclear pharmacokinetics and pharmacodynamics. The structural analysis, structure-activity relationship and drug interaction studies of ginsenosides should be the directions of future research for the development of safe and effective anti-cancer drugs. Recently, numerous studies demonstrated novel experimental, computational, and theoretical approaches for drug development. These various approaches can be utilized for developing ginsenosides as anticancer drugs. To study the side effects of ginsenosides as drugs, bioinformatics analysis can be used for the compound-protein interactions in cellular networks [13-19]. To study the multi-targeting of ginsenosides, currently, a hot area in the nutraceutical industry, the multi-label technique [20-25] for predicting subcellular localization can be used. To reveal the three-dimensional (3D) structure of the target proteins and the binding sites, the high-resolution NMR technique and structural bioinformatics are needed [26-33]. To identify various posttranslational modification (PTM) sites in nucleotides and proteins for treating cancers, the PseAAC and PseKNC approaches are very useful [34-42]. These various novel approaches in the medicinal chemistry field will significantly enhance anticancer ginsenoside research.

2. GINSENOSIDES IN *P. GINSENG* (ASIAN GINSENG) AND *P. QINQUEFOLIUS* (AMERICAN GINSENG)

Ginsenosides were first identified as key active ingredients in *P. ginseng* and subsequently found in *P. quinquefolius*. Ginsenoside content in the plant depends on the plant species, the age of the plant, and cultivated or wild populations [43]. Although the root is the most commonly used medicinal part of ginseng, ginsenosides have been detected in the entire plant, including root, stem, leaves, bud, berries, and seeds [44]. Rare ginsenosides are usually not naturally presented but can be obtained through biotransformation by various processing methods, such as steaming and microbial or enzymatic transformation [45]. To date, more than 100 ginsenosides have been discovered, including a total of 98 ginsenosides detected in *P. quinquefolius* [46].

P. ginseng and *P. quinquefolius* contain a similar ginsenoside profile. However, they vary regarding types and amount of ginsenosides. Studies have reported a higher total ginsenoside content in *P. quinquefolius* than *P. ginseng*, which suggests stronger anticancer potential [46, 47]. In both *P. ginseng* and *P. quinquefolius*, the most abundant ginsenosides are Rb1, Rb2, Rc, Rd, Re, and Rg1. The American Botanical Council (ABC) led a multi-institution Ginseng Evaluation Program ultimately reporting that the ginsenosides Rb1, Rb2, Rc, Rd, Re, and Rg1 represent more than 90% of the total ginsenosides of *P. ginseng* whereas ginsenosides Rb1, Rb3, Rc, Rd, Re, and Rg1 make up more than 70% of total ginsenosides of *P. quinquefolius* [48-50]. However, a higher ratio of Rg1 to Rb1 was found in *P. ginseng* compared with *P. quinquefolius*. In addition, the ginsenoside Rf is found exclusively in *P. ginseng* while F11 is unique to *P. quinquefolius*. Thus the ratio of Rf/F11 serves as a phytochemical marker to distinguish *P. ginseng* and *P. quinquefolius* [51, 52]. Some of the ginsenosides that are found in *P. ginseng* and *P. quinquefolius* are listed in Table **1**.

Ginsenosides have a dammarane triterpenoid structure [45]. They can be classified into four main groups Protopanaxadiol-type (PPD), Protopanaxatriol-type (PPT), Oleanolic acid-type, and Ocotillol-type, based upon their steroid backbone and the number of sugar moieties or hydroxyl groups attached (Fig. **1**). PPD and PPT are the major groups and make up the most reported ginsenosides; the main structural difference between them being the presence of a hydroxyl group and sugar moieties at C-6 in the PPT [53, 54].

2.1. Protopanaxadiol-type (PPD)

PPD-type ginsenosides include commonly reported ginsenosides Rb1, Rb2, Rb3, Rc, Rd, and rare ginsenosides Ra1, Ra2, Ra3, Rg3, Rh2 [53-55]. More than 30 PPD-type ginsenosides belong to the Rb series [56]. The metabolic pathways of the PPD-type ginsenosides have been investigated extensively. Compound K, which is the active metabolite from major ginsenosides, also belongs to this group.

Table 1. Origin of ginsenosides.

Ginsenoside	*P. ginseng* (Asian ginseng)	*P. quinquefolius* (American ginseng)	References
(20E)-F4	Y	Y	[59]
25-OH-PPD	Y	-	[60]
F1	Y	Y	[59]
F11	-	Y	[61]
Floralquinquenoside A,B,C,D,E	-	Y	[58]
Quinquifoloside-Lc	-	Y	[62]
Ra1	Y	Y	[59]
Ra2	-	Y	[63]
Ra3	Y	-	[64]
Rb1	Y	-	[65, 66]
Rb2	Y	Y	[50, 67]
Rb3	Y	Y	[59, 68]
Rc	Y	Y	[50, 59]
Rd	Y	Y	[50, 59, 69]
Rf	Y	Y	[66]
Rg1	Y	Y	[50, 70]
Rg2	Y	Y	[70]
Rg3	Y	Y	[70]
Rg5	Y	Y	[59, 71]
Rg8	-	Y	[72, 73]
Rh1	Y	Y	[74]
Rh2	Y	Y	[49, 59]
Rk2	Y	-	[59]
Rk3	Y	-	[59]
Ro	Y	Y	[69]

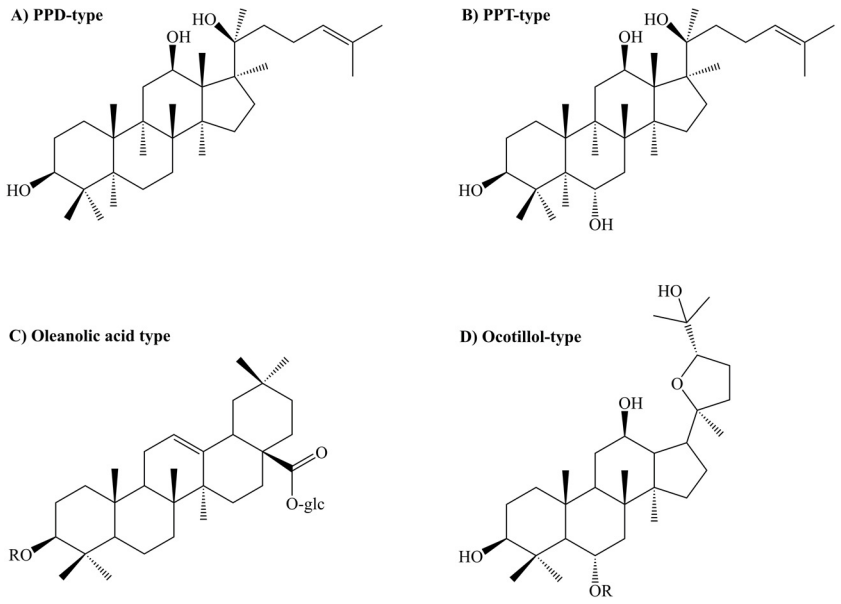

Fig. (1). Classification and chemical structure of four major groups of ginsenosides.

2.2. Protopanaxatriol-type (PPT)

PPT-type ginsenosides include Re, Rf, Rg1, Rg2, and Rh1 [57].

2.3. Oleanolic Acid-type

Ginsenosides that have a pentacyclic triterpene skeleton such as Ro are classified into this group [7].

2.4. Ocotillol-type

Ginsenosides in this group exhibits a five-membered epoxy ring at C-20, such as rare ginsenoside F11 [58].

3. REPORTED ANTI-BREAST CANCER ACTIVITIES OF GINSENOSIDES

Despite the fact that many types of ginsenosides have been identified as either naturally occurring or transformed compound, we found that there is a selective group of ginsenosides, summarized in Table **2**, that has drawn more attention from researchers and been more intensively studied for their anti-breast cancer activities. Among them, Rg3 (25 studies), Rh2 (10 studies), Rd (4 studies), and compound K (3 studies) are four ginsenosides that have received significant focus in the past eight years. Rd is one of the major ginsenosides that are abundant in both *P. ginseng* and *P. quinquefolius*. Rg3 and Rh2 are less abundant ginsenosides that are found only in red ginseng, which is prepared using a steaming process. The steaming process affects the ginsenoside profile by decreasing the major ginsenosides Rb1, Rb2, Rb3, Rc, Rd, Re, and Rg1 and increasing specific ginsenosides Rg2, Rg3, Rg5, Rh1, Rh2, and Rh4 [55]. Compound K is an *in vivo* metabolite of natural ginsenosides. Following Rg3, Rh2, Rd, and Compound K, the other ginsenosides that have shown anti-breast cancer activities in recent studies are Rg1, Rg5, Rh4, Rp1, F2, 20(S)-PPD, and 25-OCH3-PPD.

It is reported that the stereoisomers 20(S)- and 20(R)-ginsenosides possess different pharmacological effects. 20(S)- and 20(R)-ginsenosides represent 1:1 ratio in red ginseng [75], and the structural difference between 20(S)- and 20(R)- ginsenosides is based on the position of the C-20 hydroxyl group. Studies have shown that 20(R)-Rg3 displayed a superior inhibitory activity than 20(S)-isomer again breast cancer [76] (Chen *et al.,* 2008b; Yue *et al.,* 2006). However, studies have shown that many other 20(S)-ginsenosides had stronger cytotoxicity than their 20(R)-isomers [77].

Most anti-breast cancer studies included in this review focused on *in vitro* assays using breast cancer cell lines MCF-7 and triple-negative breast cancer (TNBC) cell lines MDB-MA-231, -453, -468, and 4T1. A few groups studied the inhibition of multidrug resistance using cell lines MCF-7/Adr or MCF-7/Dox. Eleven out of 47 studies were conducted using the *in vivo* xenograft mouse model. Most impressively, two clinical studies on Rg3 found effectiveness on advanced breast cancer and TNBC. Both studies found that treatment with Rg3 enhanced the anticancer effect of chemotherapeutic agents, namely Capecitabine, Docetaxel, and Cisplatin, reduced the side effects of chemotherapy through improved immune function, and improved the quality of lives of the advanced breast cancer patients.

4. MOLECULAR MECHANISM OF ANTI-BREAST CANCER ACTIVITIES

4.1. Modulation of Cancer Cell Growth and Cell Death

Several recent studies demonstrated that ginsenoside Rg3 significantly inhibited cell growth and induced apoptosis in MDA-MB-231 and MCF-7 breast cancer cells [78-83]. Peng *et al.* showed that Rg3 disturbed the expression of mammaglobin-A (MGBA) to promote cell apoptosis through the PI3K/Akt signaling pathway [81]. Alternatively, Sun *et al.* believed that the growth inhibition and apoptosis induction effects of Rg3 were related to the enhancement of MGBA expression and activation of hydrogen sulfide (H2S) /cystathionine γ-lyase (CSE) pathway [82]. Kim's findings suggest that Rg3 induced apoptosis is mediated by blocking NF-κB signaling *via* inactivation of ERK and Akt as well as destabilization of mutant p53 [79, 80]. Zou *et al.* reported Rg3 regulated phosphorylation of proteins involved in protein synthesis, cell division, and inhibition of NF-κB signaling [84]. Oh *et al.* reported that Rg3 and red ginseng extract of *Panax ginseng* (RGE) suppress breast cancer stem cells (CSCs)–like properties in MCF-7 cells through the blockade of Akt-mediated self-renewal signaling and attenuation of the expression of Sox-2 and Bmi-1, two molecular markers in stem-like breast cancer cells [85]. Rg3 also regulated the mRNA expression of autophagy signaling pathway factors LC3-II/LC3-I, p62, mTOR, PI3K, Akt, JNK, and Beclin-1 in tumor tissue of MCF-7 tumor-bearing mice [86]. Additionally, 20(R)-Rg3 was reported to inhibit MCF-7 cell proliferation *via* induction of autophagy and the release of cytochrome C from mitochondria [87, 88].

Kim *et al.* found that ginsenoside Rg5 promoted cell apoptosis dose-dependently in MCF-7 and MDA-MB-453 breast cancer cell lines with higher potency compared to 20(S)-Rg3. Rg5 regulated the expression of apoptosis-related proteins Bax, PARP, and Cytochrome C [89].

Ginsenoside Rd inhibited the proliferation and survival of MCF-7 cells and enhanced caspase-3 activity and mitochondrial depolarization, increased sub-G_1 populations, inhibited melastatin type transient receptor potential 7 (TRPM7)-like currents in MCF-7 cells [90].

Ginsenoside F2 induced apoptosis in CSCs by activating the intrinsic apoptosis pathway to induce protective autophagy in breast CSCs [91].

Ginsenoside Rh2 significantly inhibited the viability and induced apoptosis of MCF-7 and MDA-MB-231 cells *in vitro*, and induced apoptosis of MDA-MB-231 xenografts *in vivo* by down-regulation of antiapoptotic proteins Bcl-2, Bcl-xL, and Mcl-1 and up-regulation of the proapoptotic proteins Bak, Bax, and Bim *in vitro* and in tumor tissue [92].

Ginsenoside Rh4 effectively inhibited proliferation and induced apoptosis in MCF-7 cells *in vitro* and *in vivo*. The apoptosis-inducing effects of Rh4 were associated with the external apoptosis pathway by decreasing Bcl-2 and activating Bax, caspase-8, -3, and PARP [93].

Table 2. Summary of the anti-breast cancer activities of ginsenosides (2010-2018).

Ginsenoside	Anti-breast Cancer Activity	Cell Line	*In Vivo/ in Vitro*	Type of Mechanism	Signaling Pathway	Refs.
Rd	Reversed Adriamycin resistance of cells.	MCF-7/Adr	*In vitro*	Inhibition of multidrug resistance	↑ubiquitination of Multidrug resistant 1 (MDR1)	[119]
	Inhibited cell proliferation; induced apoptosis.	MCF-7	*In vitro*	Modulation of cell growth & cell death	↑TRPM7 channel activity	[90]
	Decreased the volume and weight of xenograft tumors; inhibited VEGF-induced migration, tube formation and proliferation of HUVECs; induced apoptosis.	MDA-MB-231; MCF-7; MDA-MB-468	*In vivo/in vitro*	Inhibition of angiogenesis	↓Akt/mTOR/P70S6 kinase signaling	[111]
	Suppressed cell migration and invasion *in vitro*; decreased number of lung tumor lesions *in vivo*.	4T1	*In vivo/in vitro*	Inhibition of metastasis	↓miR-18a-mediated Smad2 expression regulation	[115]
Rg1	Supressed cells invasion and migration	MCF-7	*In vitro*	Inhibition of metastasis	↑NF-kB pathway; ↓MMP-9	[116]
Rg3	Inhibited proliferation and induced apoptosis.	MCF-7/Adr	*In vitro*	Modulation of cell growth & cell death	Alter the phosphorylation of proteins involved in protein synthesis, cell division; ↓NF-κB signaling	[84]
	Inhibited cell migration.	MDA-MB-231	*In vitro*	Inhibition of metastasis	↓CXCR4	[82]
	Inhibited proliferation and induced apoptosis.	MDA-MB-231	*In vitro*	Modulation of cell growth & cell death	↓MGBA ↓PI3K/Akt signaling pathway	[81]
	Inhibited proliferation and formation of tube-like structure.	MCF-7	*In vitro*	Inhibition of angiogenesis	↓VEGF-A, MMP-9 & HIF-1α	[107]
	Inhibited proliferation and invasion; induced the apoptosis; arrested cell cycle.	MCF-7	*In vitro*	Modulation of cell growth, cell death & cell cycle; Inhibition of metastasis	↓MMP-9	[78]
	Inhibited the growth and invasion.	MDA-MB-231	*In vitro*	Modulation of cell growth & cell death; Inhibition of metastasis	-	[83]
	Inhibited cell growth; arrested cell cycle.	MDA-MB-231	*In vitro*	Modulation of cell growth & cell death	↓Cyclin E & CDC25A	[103]
	Inhibited cell growth; arrested cell cycle.	anoikis-resistant MCF-7	*In vitro*	Modulation of cell growth & cell death	-	[101]
	Inhibited proliferation; induced apoptosis.	MDA-MB-231	*In vitro*	Modulation of cell growth & cell death	↑MGBA; ↑H2S/CSE system	[82]
	Inhibited proliferation; induced apoptosis.	MDA-MB-231	*In vitro*	Modulation of cell growth & cell death	↑mitochondria-dependent caspase	[79]
	Inhibited proliferation; induced apoptosis.	MDA-MB-231	*In vitro*	Modulation of cell growth & cell death	↓NF-κB signaling; ↓ERK/ Akt; destabilization of mutant p53	[80]

(Table 2) contd….

Ginsenoside	Anti-breast Cancer Activity	Cell Line	*In Vivo/ in Vitro*	Type of Mechanism	Signaling Pathway	Refs.
	Inhibited proliferation; induced apoptosis.	MCF-7/Adr	*In vitro*	Modulation of cell growth & cell death	↓Cyclin E & CDC25A	[102]
	Postponed the occurrence of Tamoxifen resistance.	MCF-7	*In vitro*	Inhibition of multidrug resistance	-	[118]
	Decreased the cell viability and suppressed breast cancer stem cells (CSCs)–like properties.	MDA-MB-231; MCF-7	*In vitro*	Inhibition of metastasis	↓Akt-mediated self-renewal signaling; ↓Sox-2 and Bmi-1	[85]
	Inhibited tumor growth; reduced toxic side effects; improve the life quality.	-	*In vivo*	Inhibition of angiogenesis	-	[108]
	Inhibited tumor growth.	-	*In vivo*	Inhibition of angiogenesis & Modulation of cell cycle	↓Cyclin E, CDC26A; ↓VEGF, bFGF	[98]
	Reduced tumor volume on tumor-bearing mice; inhibited angiogenesis and cell invasion; enhanced cell autophagy.	MCF-7	*In vivo*	Inhibition of angiogenesis	-	[86]
	Reduced the number of tumor nodules and lung weight in the metastasis mice model.	4T1	*In vivo*	Inhibition of metastasis	↓MMP-2, VEGF	[113]
	Inhibited tumor growth on nude mice; arrested cell cycle.	MCF-7	*In vivo*	Modulation of cell growth & cell death; Inhibition of angiogenesis	↓VEFG, MMP-2, MMP-9	[99]
	Inhibited tumor growth in nude mice; arrested cell cycle.	MDA-MB-231	*In vivo*	Modulation of cell growth & cell death	↓proCaspase-3 and procaspase-9	[109]
	Enhanced the clinical anticancer effects of Docetaxel and Cisplatin; improved the life quality of advanced breast cancer patients.	-	*Clinical trial*	Cancer immune-modulation	-	[127]
	Improved the anticancer effect of capecitabine and reduced the chemotherapeutic side effects.	-	*Clinical trial*	Cancer immune-modulation	-	[128]
20(R)-Rg3	Improved the anticancer effect of chemotherapy and reduced the chemotherapeutic side effects.	-	*Clinical trial*	Inhibition of angiogenesis	↓VEGF in serum	[110]
	Inhibited cell proliferation; induced autophage.	MCF-7	*In vitro*	Modulation of cell growth & cell death	-	[87]
	Induced apoptosis.	MCF-7	*In vitro*	Modulation of cell cycle	↑ mitochondria cytochrome C release	[88]
Rg5	Inhibited cell proliferation; induced apoptosis; arrested cell cycle.	MCF-7; MDA-MB-453	*In vitro*	Modulation of cell growth, cell death, & cell cycle	↓cyclin D1, cyclin E2, CDK4, ↑p15INK4B, p53, p21WAF1/CIP1	[89]
Rh2	Increased the sensitivity of cells to 5-FU.	MCF-7	*In vitro*	Modulation of cell growth & cell death	-	[100]
	Inhibited cell proliferation; reversed multidrug resistance.	MCF-7/Adr	*In vitro*	Inhibition of multidrug resistance	-	[120]

(Table 2) contd….

Ginsenoside	Anti-breast Cancer Activity	Cell Line	*In Vivo/ in Vitro*	Type of Mechanism	Signaling Pathway	Refs.
	Decreased cell viability; induced apoptosis; reversed drug resistance.	MCF-7; MCF-7/Dox; MCF-7/Adr	*In vitro*	Inhibition of multidrug resistance	↓miR-29a, miR-222 and miR-34a	[122]
	Enhanced immunogenicity; inhibited cell growth.	MCF-7	*In vitro*	Cancer immune-modulation	↑epigenetic methylation changes in genes involved in immune response and tumorigenesis	[129]
	Enhanced sensitivity to adriamycin and fluorouracil.	MCF-7/Adr	*In vitro*	Inhibition of multidrug resistance	↓drug-resistant protein P-gp	[121]
	Decreased the cell-ground substance adhesion ability, invasion and migration.	MCF-7/Adr	*In vitro*	Modulation of metastasis	↓PI3K/AKT signaling pathway	[117]
	Inhibited cell viability and induced apoptosis *in vitro* & *in vivo.*	MDA-MB-231; MCF-7	*In vitro/in vivo*	Modulation of cell growth & cell death	↓antiapoptotic proteins Bcl-2, Bcl-xL, Mcl-1;↑proapoptostic proteins Bak, Bax, Bim	[92]
	Inhibited the growth of drug-resistant xenograft tumor.	MCF-7	*In vivo*	Inhibition of metastasis	↑P-gp ATPase activity	[125]
20(S)-Rh2	Reversed Adriamycin resistance.	MCF-7/Adr	*In vitro*	Inhibition of multidrug resistance	↓P-gp	[123]
	Reversed Adriamycin resistance.	MCF-7/Adr	*In vitro*	Inhibition of multidrug resistance	↓MAPK/NF-β pathway; ↓adriamycin-induced ABCB1 expression	[122]
Rh4	Inhibited cell proliferation; arrested cell cycle; induced apoptosis *in vitro*; inhibited tumor growth *in vivo.*	MCF-7	*In vitro/in vivo*	Modulation of cell growth & cell death	↓Bcl-2; ↑Bax, caspase-8, -3, PARP	[93]
Rp1	Inhibited cell proliferation; induced apoptosis.	MCF-7; MCF-7/Dox; MDA-MB-231; T-47D	*In vitro*	Modulation of cell growth & cell death	↓IGF-1R/Akt pathway	[94]
20(S)-Protopanaxadiol (PPD)	Inhibited cell proliferation; induced apoptosis.	MDA-MB-231	*In vitro*	Modulation of cell growth & cell death	↑caspase-dependent apoptosis pathway	[104]
	Inhibited cell proliferation; induced apoptosis.	MCF-7	*In vitro*	Modulation of cell growth & cell death	↑caspase-dependent apoptosis pathway	[106]
F2	Induced apoptosis & autophagy.	Breast cancer stem cells (CSC)	*In vitro*	Modulation of cell growth & cell death	↑intrinsic apoptosis pathway	[91]
25-OCH3-PPD	Inhibited cell growth; inhibited cancer cell migration; induced apoptosis in xenograft tumors.	MDA-MB-468; MCF-7	*In vivo/in vitro*	Inhibition of metastasis	↓MDM2 oncogene	[114]
Compound K	Inhibited proliferation, migration and invasion.	MCF-7	*In vitro*	Modulation of cell growth & cell death	↓MMP-2 & MMP-9	[95]
	Inhibited cell proliferation and epithelial mesenchymal transition; induced apoptosis.	MCF-7	*In vitro*	Modulation of cell growth & cell death	↓PI3K/Akt pathway	[96]
	Inhibited cell proliferation; induced programmed necrosis.	MCF-7	*In vitro*	Modulation of cell growth & cell death	↓GSK3β signaling pathway.	[97]

Ginsenoside Rp1 inhibited the proliferation and cell colony formation of MCF-7, MCF-7/DOX, MDA-MB-231, and T-47D breast cancer cells *in vitro* by down-regulation of the IGF-1R/Akt pathway [94].

Compound K inhibited proliferation and induced apoptosis in MCF-7 cells [95, 96]. Compound K reduced the levels of N-cadherin, vimentin, p-Akt/Akt, and elevated the level of E-cadherin, thus indicating that Compound K exerted its anti-proliferation effect *via* the PI3K/Akt pathway [96]. Interestingly, another study demonstrated that Compound K inhibited MCF-7 cell proliferation by inducing programmed necrosis, but not apoptosis, *via* the GSK3β signaling pathway [97].

It is worth mentioning that the ginsenosides showed a synergetic effect in the combination with chemotherapeutic agents, such as Rh-endostatin, 5-FU, and cisplatin. Two independent studies found that the administration of Rg3 in combination with Rh-endostatin in breast tumor-bearing nude mice resulted in a synergetic effect on inhibiting tumor growth compared with applying Rg3 or Rh-endostatin alone [98, 99]. The more recent study by Li *et al.* also found that this combination has a superior effect on inhibition of VEGF, MMP-2, MMP-9 expression and arrest of the cell cycle [99]. Feng *et al*. reported that ginsenoside Rh2 increased the apoptosis effect of 5-FU on MCF-7 cells by increasing the sensitivity of MCF-7 cells to 5-FU [100]. The combination of Compound K with cisplatin produced a superior cytotoxic effect in MCF-7 cells [96].

4.2. Modulation of Cell Cycle

Several studies on Rg3 consistently showed that Rg3 affects the cell cycle of breast cancer cells both *in vitro* and *in vivo*. Chen *et al.* reported that Rg3 inhibited the proliferation of MCF-7 cells by decreasing the percentage of cells in G_0/G_1 and S phase, whereas increasing the percentage of cells in G_2/M [78]. Rg3 significantly inhibited the growth of Anoikis-resistant MCF-7 cells by arresting the cell cycle in the G_0/G_1 phase [101]. Rg3 also inhibited the proliferation of Adriamycin-resistant MCF-7 cells by decreasing the expression of cell cycle-associated factors Cyclin E and CDC25A [102]. Combined administration of Rg3 with Rh-endostatin in breast tumor-bearing nude mice suppressed Cyclin E and CDC25A and arrested the cell cycle in tumor tissue [98, 99]. Similarly, Pan *et al.* reported Rg3 inhibited the growth of MDA-MB-231 by down-regulating Cyclin E and CDC25A [103].

Ginsenoside Rg5 induced cell cycle arrest in the G_0/G_1 phase through regulation of cell cycle-related proteins in MCF-7 and MDA-MB-453 breast cancer cells, *i.e.,* increasing the expression of p53, $p21^{WAF1/CIP1}$ and $p15^{INK4B}$ and decreasing the expression of Cyclin D1, Cyclin E2 and CDK4 [89]. Ginsenoside Rh4 arrested the cell cycle in the S phase in MCF-7 cells *in vitro* [93]. Ginsenoside Rp1 induced cycle arrest in MCF-7, MCF-7/DOX, MDA-MB-231, and T-47D breast cancer cells [94].

The ginseng sapogenins 20(S)-protopanaxadiol (PPD), 20(S)-protopanaxatriol, 20(S)-dihydro-protopanaxadiol, and 20(S)-dihydro-protopanaxatriol suppressed the proliferation of MDA-MB-231 cells. PPD showed the highest potency and induced dose-dependent cleavage of caspase-3, -8, and PARP in the cells [104]. Consistently, another study showed that PPD inhibited proliferation and induced apoptosis of MCF-7 cells by inducing caspase-mediated apoptotic cell death [105].

4.3. Inhibition of Angiogenesis

The growth, spread, and metastasis of tumors are closely related to the formation of tumor blood vessels. The nutrients and oxygen required for tumor cell growth depend on the supply of new blood vessels in tumor tissues. Meanwhile, tumor cells enter the blood circulation through unsound blood vessels and metastasize to distant organs. Administration of drugs to block the formation of tumor angiogenesis has been accepted as one of the most critical approaches to control tumor growth and metastasis [76]. Some studies on ginsenosides Rg3 and Rd displayed their potentials as angiogenesis suppressor of breast tumors [106].

Rg3 suppressed the proliferation of MCF-7 cells and significantly reduced the number of tube-like structures in a dose-dependent manner. Rg3 also inhibited the vasculogenic mimicry of MCF-7 cells by modulating angiogenesis factors vascular endothelial growth factor A (VEGF-A), MMP-9, and hypoxia-inducible factor 1α (HIF-1α) protein [107]. In an *in vivo* study, Rg3 combined with Endostar (human endostatin) enhanced the reduction of tumor tissue volume in MCF-7 tumor-bearing mice. Similar to endostatin, Rg3 reduced the mRNA expression angiogenesis factors VEGF, MMP-2 and MMP-9 in tumor tissue [99]. In another *in vivo* study on MCF-7 tumor-bearing nude mice, administration of Rg3 combined with arsenic trioxide resulted in stronger inhibition to the tumor growth, neoangiogenesis, and microvascular density in tumor tissue. Rg3 also reduced the toxic side effects and improved the life quality of the mice in this experiment [108]. In addition, Rg3 inhibited MDA-MB-231 tumor growth in nude mice by induction of tumor cell apoptosis [109].

In a clinical trial, 20(R)-Rg3 combined with chemotherapy (cytoxan and doxorubicin) achieved better therapeutic effects and fewer side effects compared to chemotherapy alone. The combined therapy decreased the VEGF level in the patients' serum, which indicated that the anticancer effects of 20(R)-Rg3 might be related to reducing angiogenesis in tumor tissue [110].

Intraperitoneal administration of Rd decreased the volume and weight of solid tumors formed by mice bearing MDA-MB-231 cell xenografts and reduced tumor angiogenesis as evidenced by less Ki67- and CD31-positive cells. The *in vitro* assay demonstrated that Rd inhibited VEGF-induced migration, tube formation and proliferation of HUVECs dose-dependently, induced apoptosis and inhibited Akt/mTOR/P70S6 kinase signaling in MDA-MB-231, MCF-7, and MDA-MB-468 cells [111].

4.4. Inhibition of Metastasis

Tumor metastasis remains the primary cause of mortality or poor prognosis in breast cancer patients. About 90% of mortality occurs due to invasion and metastasis in the advanced stages of breast cancer. Anti-metastatic therapies are

in great need to achieve the optimal clinical outcome in breast cancer patients. Recent studies showed the effectiveness of some ginsenosides in the inhibition of metastasis *in vitro* and *in vivo*, indicating their potential to be anti-metastatic agents for human breast cancer.

Ginsenoside Rg3 decreased the cell invasion index in a time and dose-dependent manner and suppressed the expression of MMP-9 in MCF-7 cells [78]. Similarly, Rg3 significantly decreased the invasion index of MDA-MB-231 breast cancer cells [83]. In a non-toxic concentration, Rg3 inhibited the expression of C-X-C chemokine receptor type 4 (CXCR4), a vital molecule in metastasis of cancer cells, and inhibited chemotaxis elicited by CXCL12, the CXCR4 ligand in MDA-MB-231 cells. This study revealed that Rg3 is a direct CXCR4 inhibitor in cancer metastasis [112]. Additionally, Rg3 significantly reduced the number of tumor nodules and lung weight in the mice 4T1 cell metastasis model, which is associated with inhibition of the expression of MMP-2 and VEGF in the serum and lung tissue [113].

Wang *et al.* found that 20(S)-25-methoxyldammarane-3b, 12b, 20-triol (25-OCH_3-PPD) inhibited cell survival and migration in MCF-7 and MDA-MB-231 cells *in vitro* and prevented tumor metastasis in nude mice bearing MCF-7 or MDA-MB-468 xenograft tumors *in vivo*. The mechanisms of action of 25-OCH_3-PPD included inducing apoptosis and G_1 phase arrest, reducing the expression of epithelial-to-mesenchymal transition (EMT) markers, and down-regulating MDM2 oncogene [114].

Rd suppressed cell migration and invasion in 4T1 cells dose-dependently and decreased the number of lung tumor lesions in both spontaneous and metastasis mice models. Moreover, Rd increased the expression of Mothers against decapentaplegic homolog 2 (SMAD2) and decreased the expression of microRNA-18a (miR-18a) in 4T1 cells and 4T1 cell-inoculated tumors in mice. This suggests that Rd attenuates breast cancer metastasis through depressing miR-18a-mediated SMAD2 expression regulation [115].

Rg1 suppressed phorbol myristate acetate (PMA)-induced MCF-7 cell invasion and migration by regulating the NF-κB pathway to inhibit the expression of MMP-9 [116].

Piao *et al.* showed that Rh2 decreased the cell-ground substance adhesion ability and the cell invasion and migration through the suppression of the PI3K/AKT signaling pathway in MCF7/Adr breast cancer cells [117].

Sun *et al.* reported Compound K inhibited the proliferation, migration and invasion ability of the MCF-7 cells, which is relevant to the decreased expression of MMP-2 and MMP-9, two primary factors related to the migration and invasion of cancer cells [95]. Compound K also inhibited the epithelial-mesenchymal transition in MCF-7 cells [95, 96].

4.5. Inhibition of Multidrug Resistance

A major challenge in the treatment of breast cancer is the development of broad anticancer drug resistance by tumor cells that are termed as multidrug resistance (MDR). Among all ginsenosides, Rg3, Rd, and Rh2 are found to display the most potential in reversing MDR in breast cancer. These ginsenosides combined with chemotherapy might be useful to reduce the drug resistance incidence in clinical practice.

Rg3 was shown to possess the activity of inhibiting drug resistance. Rg3 postponed the occurrence of Tamoxifen resistance in MCF-7 cells [118]. Two studies have reported that Rg3 significantly inhibited the growth of anoikis-resistant MCF-7 cells [101] and Adriamycin-resistant MCF-7 cells [102].

Rd was reported to reverse the doxorubicin resistance in Adriamycin-resistant MCF-7 (MCF-7/Adr) cells by increasing the ubiquitination of MDR1 protein in the cells [119].

The treatment of Rh2 in combination with Adriamycin at non-effect dosage resulted in higher inhibitory efficacy and increased cell-death velocity, suggesting the effectiveness of Rh2 in reversing multidrug resistance in MCF-7/Adr cells [120]. In another study, Rh2 enhanced the sensitivity of MCF-7/Adr to Adriamycin and Fluorouracil, two commonly used chemotherapy medicines, while significantly inhibiting the cell drug-resistant protein P-glycoprotein (P-gp) [121]. Additionally, Wen *et al.* suggested that the drug resistance reversal effect of Rh2 on MCF-7/Adr could be due to the regulation of specific microRNA expression [122]. Zhang *et al.* showed that 20(S)-Rh2 reversed Adriamycin resistance of MCF-7/Adr cells by inhibiting P-gp activity [123] and regulating MAPK/NF-κB pathway to decrease Adriamycin-induced ATP-binding cassette B1 (ABCB1) expression [124]. Qu *et al.* developed a multicomponent microemulsion consisted of etoposide, coix seed oil, and ginsenoside Rh2 (ECG-ME), for oral delivery of etoposide to treat multidrug-resistant breast cancer in xenograft mouse models and observed synergistic antitumor activity of these ingredients in ECG-ME [125].

4.6. Cancer Immune-modulation

The post-surgery treatment of malignant tumors is essential in preventing tumor recurrence. Recent studies showed that immunomodulators have positive effects on avoiding tumor relapse. Ginsenosides have been studied intensively for their immunomodulatory effects. In Asia, ginseng has been widely used for the management of chemotherapy-induced side effects, such as nausea, loss of appetite, and fatigue. Some clinical trials demonstrated that ginsenosides or ginsenoside-containing extracts in combination with chemotherapy improve the immune function and increase the lifespan of cancer patients after surgery [126]. However, the role that ginsenoside serves in anti-breast tumor immunological activity remains to be elucidated, and literature in this field is quite limited.

Zhang *et al.* observed the clinical effects of Shenyi Capsule (with Rg3 as the active ingredient) combined with Docetaxel and Cisplatin on advanced breast cancer patients and found that this combination enhanced the clinical anticancer effects and significantly improved the life quality of the patients [127]. Li observed in the clinical trial that the combined oral administration of Rg3 and Capecitabine in patients with advanced triple-negative breast cancer improved the anticancer effect and reduced the side effects of chemotherapy compared to a single application of Capecitabine [128]. These two reports suggested that the advantage of

general immunity improvement might be the anticancer mechanism of Rg3.

In addition, Lee *et al*. reported that Rh2 induced epigenetic methylation of genes involved in immune response and tumorigenesis in MCF-7 cells, thereby contributing to enhanced immunogenicity and growth inhibition [129].

As with other natural product research, the current research on ginsenosides has encountered obstacles such as multiple targets, complex mechanisms of action, and unclear pharmacokinetics and pharmacodynamics. Future research for the development of ginsenosides as safe and effective anti-cancer drugs should focus on their structural analysis, structure-activity relationship, and *in vivo* drug interaction studies.

CONCLUSION

Our understanding of the anticancer properties of ginseng has advanced over the past eight years in conjunction with the discovery of novel ginsenoside compounds. Ginseng is widely used as complementary medicine in the treatment or post-surgery management of cancer patients in Asia. Based on our review, ginsenosides, which are the main active constituents of ginseng, have potential as anti-breast cancer agents because of their antiproliferative, anti-metastasis, and tumor immunomodulation activities. Ginsenosides exhibit diverse molecular mechanisms of action by regulating the most known modulators of cell growth, cell death, cell cycle, multidrug resistance, and metastasis, *etc.* Among all ginsenosides, Rg3 and Rh2 attracted the most research interest regarding ginseng's potential anti-breast cancer effects. In summary, recent advances in the evaluation of ginsenosides as therapeutic agents against breast cancer support further pre-clinical and clinical studies to treat primary and metastatic breast tumors.

Because of the tremendous findings and promise of ginsenosides as anticancer agents, we believe that the development of a web-server information repository is a valuable next step. Web-servers are playing an increasingly important role in compiling phytochemicals and accelerating *in silico* drug discovery from natural products. Currently, there are several sources of publicly available web servers for phytochemicals, such as Phytochemica [130], NPACT [131], and Herb Ingredients' Targets [131]. A publicly available platform targeting ginsenoside research with a user-friendly interface will accelerate the process of lead identification from ginseng and will serve as an advantageous source benefiting the research community.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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