Cancer Prevention and Therapeutics: *Panax Ginseng*

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Abstract

***Panax ginseng* has been used as a medicinal plant in China for thousands of years. Current use in Western countries has been diverse, with focused research on cancer therapeutics. *P. ginseng* apparently mitigates cancer through anti-inflammatory, antioxidant, and apoptotic mechanisms to influence gene expression. Additional mechanisms of investigation include influence on neurotransmission and immunosurveillance. Low toxicity and positive studies in concomitant use with other chemotherapeutic agents is promising. Although there is no conclusive evidence of *P. ginseng* curing cancer, research has continually found tumor inhibition, especially in the promotion and progression phases.**

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Introduction

The root and rhizome of *Panax ginseng* C.A. Meyer (Araliaceae) has been used as a medicine by the people of Eastern Asia for at least 2,000 years. Native to Korea and northeastern China, this red-berried plant, commonly called Korean ginseng, is now cultivated throughout the world. It appears in the pharmacopoeias of several countries including China, Japan, Germany, Austria, the United Kingdom, and France, and is often employed for cancer, diabetes mellitus, and cardiovascular concerns. As in the past, *P. ginseng* is still thought of as a panacea, perpetuated by its name panax, meaning "cure all" in Greek. For these reasons *P. ginseng* is one of the most sought-after medicines throughout the world. It was the second-highest selling herbal supplement in the United States in 2000, with gross retail sales of $US62 million.[1]

Many herbal products are often mistakenly called ginseng. These include *P. quinquefolium* (American ginseng), from the northeastern parts of the United States and Canada; *P. notoginseng*, from Yun-nan Province in China and northern Vietnam; *P. vietnamensis*, from central Vietnam; *P. japonicus*, from Japan; and *P. pseudoginseng*, from the Himalayan region. Adding to the confusion, other botanical medicines are commonly called ginseng that do not belong to the same family as *P. ginseng* – *Eleutherococcus senticosus* (Siberian ginseng) and *Pfaffia paniculata* (Brazilian ginseng). Each so-called "ginseng," however, ranges widely in both similarity and disparity to the constituents of *P. ginseng*, and despite any overlap observed in their actions, the traditional uses and more current studies illuminate many distinctive therapeutic applications.

Biochemistry

The active principals of *P. ginseng* include saponins, polysaccharides, flavonoids, and volatile oils. In cancer therapeutics the saponins and polysaccharides have engendered the greatest investigation.

Acidic polysaccharides (10,000-150,000 MW) have been observed to have immunomodulating and antiproliferative effects in tumor cell lines. Readily soluble in water, these polysaccharides contain various sugar moieties, uronic acid, and less than five-percent protein by weight.

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Table 1. Noteworthy Ginsenosides (28 are known)

Panaxadiols	Panaxatriols
Key Ginsenosides	
Rb1,Rb2, Rc, Rd, Rg3, Rh2	Re, Rf, Rg1, Rg2, Rh1
Metabolites	
20(S)- protopanaxadiols (i.e., 20(S)-Rg3)	20(S)- protopanaxatriols (i.e., 20(S)-Rg2 and 20(S)-Rh1)
Further Metabolites	
Compound K, M1, IH901 (20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol); Panaxydiol	Panaxytriol (heptadeca-1-ene-4,6-diyne-3,9,10-triol)

Ginseng's saponins, generally called ginsenosides (Rx), are emphasized in cancer chemoprevention and therapeutics. The primary ginsenosides and their metabolic cousins have a steroid-like structure[2,3] and are generated by acid hydrolysis of saponins[4] and human intestinal bacteria.[5-7] With the exception of ginsenoside Ro, which is an oleanane-type triterpenoid, all ginsenosides are the dammarane-type separated into panaxadiol and panaxatriol classes (Table 1).

In Asia, the traditional preparations of fresh white and red ginseng have various concentrations of ginsenosides that develop in complexity with age (Table 2) and preparation. Classically, fresh ginseng is anything picked before four years of growth. White ginseng (picked at 4-6 years) is peeled and then dried, and contains high concentrations of Rb1, Rb2, Rc, and Rd of the -diol group. Red ginseng (harvested at 6 years) traverses both ginsenoside classes speaking to liberation of new constituents – Rh1, Rh2, and Rg3 – from steaming the dry whole root.[4,8] These traditional preparations generate a therapeutic dose by stockpiling specific metabolites for direct absorption and creating a similar composite of primed metabolites for digestive processes to complex for absorption (Figure 1).

Table 2. Concentrations of Ginsenosides with Age

Years	Total Saponins (%)	Rb (%)	Rg (%)	Ro (%)
2	1.97	0.88	0.54	0.13
3	2.20	1.03	0.62	0.17
4	4.75	2.27	1.10	0.40
5	4.60	2.08	1.19	0.21
6	3.84	1.94	0.81	0.29
9	3.81	2.32	0.46	0.40

From: Liu CX, Xiao PG. Recent advances on ginseng research in China. J Ethnopharmacol 1992;36(1):27-38.

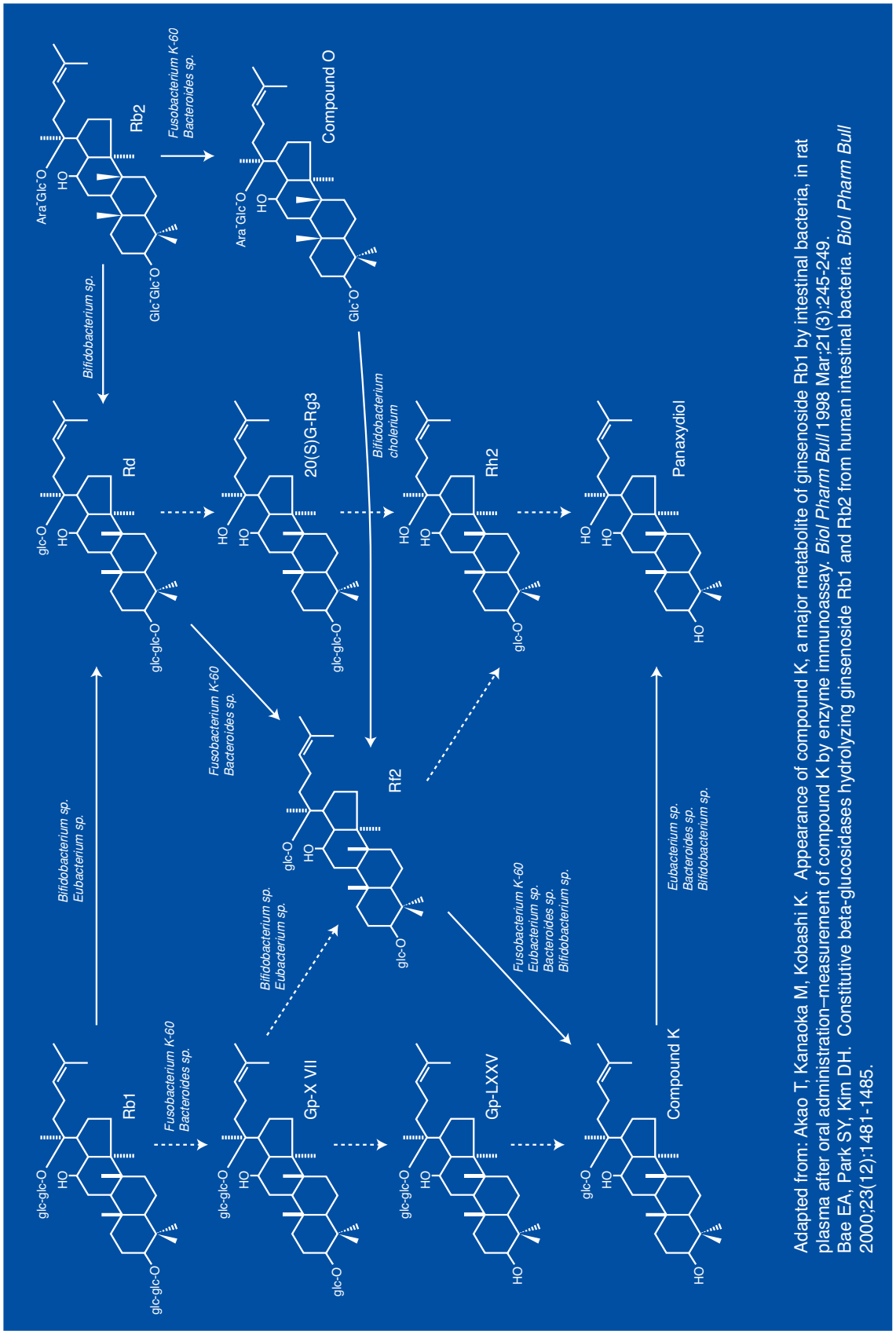
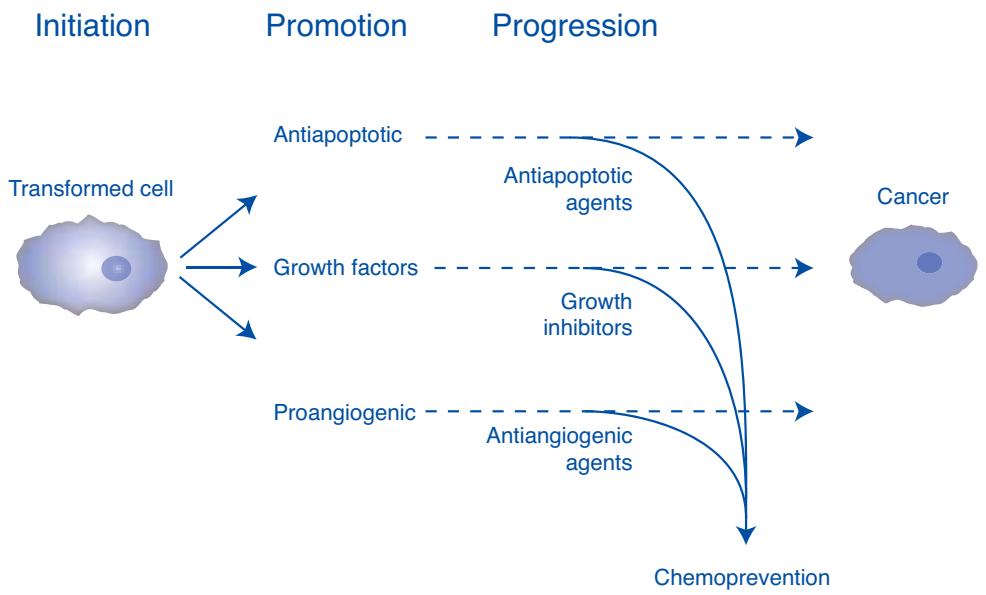


Figure 1. Metabolic Pathways of Rb1 and Rb2 by Human Intestinal Bacteria

Adapted from: Akao T, Kanaoka M, Kobashi K. Appearance of compound K, a major metabolite of ginsenoside Rb1 by intestinal bacteria, in rat plasma after oral administration–measurement of compound K by enzyme immunoassay. *Biol Pharm Bull* 1998 Mar;21(3):245-249. Bae EA, Park SY, Kim DH. Constitutive beta-glucosidases hydrolyzing ginsenoside Rb1 and Rb2 from human intestinal bacteria. *Biol Pharm Bull* 2000;23(12):1481-1485.

Figure 2. The Continuum of Carcinogenesis



Adapted from: Tsao AS, Kim ES, Hong WK. Chemoprevention of cancer. *CA Cancer J Clin* 2004;54(3):150-80.

A 1994 comparison study found that wild, harvested plants contain more of the Rg, Rd, and Re fractions, while cultivated plants possess a greater total ginsenoside content and Rb fraction.[9] In a related study, cultured tissue cells of *P. ginseng* rarely contained half the fractional constituents of the cultivated plant.[10] In 2003 the World Health Organization's new guidelines list *P. ginseng* as endangered due to overharvesting.[11] The given scarcity of natural ginsenosides has prompted the search for routes of synthesis from more accessible products. The common birch, *Betula alba* L. (Betulaceae), contains betulafolienetriol that has been used as a starting compound in at least one study to prepare semi-synthetic ginsenosides.[12]

The standardization of ginseng formulations varies in concentration from 4-7 percent ginsenosides (calculated as ginsenoside Rg1),[13] although polysaccharides may need to be added as an additional reference point in specific cancer preparations.[14] In both cases the bioavailable dose is a function of horticultural variables, preparation methods, and the interaction of individual variation of digestive processes that, in the case of ginsenosides, diversify and concentrate constituents.

Panax Ginseng and the Phases of Cancer: Mechanisms of Action

A search of PubMed for "cancer," "tumor," and "*Panax ginseng*" yields over 200 articles, signaling the progressive search for help in a society that has just been informed the current five-year survival rate with cancer is 64 percent, up from 50 percent in 1975.[15]

From the initiation of cancer, pathogenesis proceeds to promotion until progression. Initiation phase is rapid (within hours to days) where irreversible DNA changes occur that are successfully perpetuated via mitosis. Promotion stage may take years or decades to establish an actively proliferating premalignant lesion. While in the progression phase, new clones with increased proliferative capacity, invasiveness, and metastatic potential are produced within a narrow window, perhaps within a year (Figure 2).[16]

The result of successive mutations, cancer establishes a state of disharmonious intercellular communication. As the discord widens, the cell becomes less capable of inducing apoptosis (programmed cell death) to quell the escalating cellular chaos. Immune cells are therein deflected from surveillance and/or overrun by the cascade

of dividing cells, unable to restore order by inducing apoptosis or even necrosis (cell death with inflammation) in these errant cells. This cumulative loss in intracellular and intercellular communication is incremental in malignant cells and is referred to as chemotolerance. Chemotolerance first stops the cellular defenses and thereafter impedes the success of immune cells, chemotherapy, and radiation.

Fortunately, surgery has become a successful treatment for cancer, to the degree that 90 percent of cancer-related deaths are due to non-primary metastatic growths.[17] It is now understood that many of these unreachable growths develop from more than one aberrant cell line. Tumors consisting of more than one genetic cell line are explained by field carcinogenesis, which specifies that different cells within a tissue may mutate distinctively from each other due to disparities in input interpretation.[18] Subsequent post-surgical treatment may be complicated by dissimilar chemotolerance between cell lines, thwarting chemotherapy and radiation. Therefore, success in cancer care is continually dependent on development of specific and even multifaceted therapies.

Mitigating DNA Damage

Inducing Differentiation

Ginseng's induction of repair or reverse transformation of cells into more differentiated (genetically stable) cells has been noted in hepatoma,[19,20] melanoma,[21,22] and teratocarcinoma cells.[23] However, these recognized changes in gene expression have not, in and of themselves, shown promising avenues in chemoprevention or therapeutics.

Reduced Effects from Chemical Carcinogens

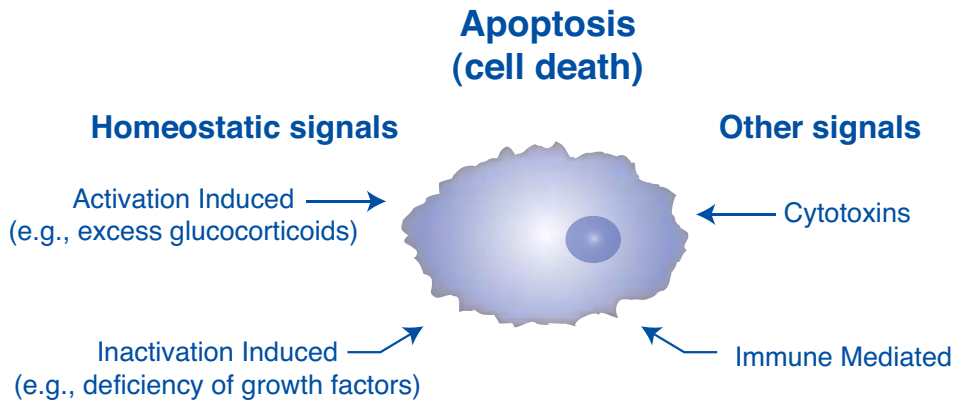
Reduction in induced carcinogenesis by various chemical carcinogens has been well documented. Yun et al found red ginseng reduced 9,10-dimethyl-1,2-benzanthracene (DMBA) cancer cell infiltration by 63 percent. With urethane exposure, red ginseng availed a 22-percent decrease in lung adenoma, while aflatoxin B_1-induced lung adenoma and hepatoma were reduced 29 and 75 percent, respectively.[24] Different ages and types of ginseng were studied with benzo(a)pyrene, noting more significant lung anticarcinogenic effects with red ginseng than fresh ginseng.[25] It was further noted that Rg3 and Rg5 demonstrated significant reductions in benzo(a)pyrene-induced adenocarcinoma, while Rh2 did not reach significance[26] Inhibition was also found in lung tumors induced by dimethylbenz(a)anthracene in mice.[27] Bespalov has shown strong inhibitory effects on the development of rat mammary adenocarcinoma induced by methyl-N-nitrosourea and N-ethyl-N-nitrosourea administration, as well as in DMBA-induced uterine and vaginal tumors.[28]

Other investigations that use inducers of cytotoxicity suggest the efficacy of *P. ginseng* extracts in cancer treatment.[29,30] Despite dose-dependent antigenotoxic properties in extracts[31] and metabolites,[32] the reasons for reduced carcinogenesis with concomitant use of *P. ginseng* are unknown, although genetic ties may have connection with ginseng's reduction in inflammation and oxidizing radicals.

Mitigating Anti-inflammatory Carcinogenesis

Repeated insult by inflammatory processes has long been implicated in all phases of cancer.[18] Cyclooxygenase-2 (COX-2), omnipresent in inflammatory processes, releases inflammatory metabolites and reactive elements, and is induced by growth factors, carcinogens, and oncogenes.[33] Recent studies have shown that the 20(S)-protopanaxatriols as well as Rg3 inhibit induced COX-2 expression. This process has been attributed to inactivation of nuclear factor-kappaB (NF-κB), a transcription factor whose activation inhibits the cell death signaling of oncogenic *ras*.[34-36] Inducible nitrous oxide synthetase (iNOS) is another inflammatory enzyme curtailed by this down-regulation of NF-κB.[37-38] Finally, a derivative of Rb1 and Rb2, often called Compound K, reduces inflammation[39] and has been found to have a stronger inhibitory effect on histamine release than disodium cromoglycate – an anti-allergy preparation.[40]

Figure 3. Signals Inciting Apoptosis



Adapted from: Eastman A. Apoptosis: a product of programmed and unprogrammed cell death. Toxicol Appl Pharmacol. 1993 Jul;121(1):160-4.

Antioxidant Chemoprevention

The antioxidant activities of *P. ginseng* also help explain its DNA-preserving qualities with respect to chemical carcinogens and inflammation. Ginseng extracts have been shown to scavenge reactive oxidative species (ROS)[41-43] as well as attenuate lipid peroxidation.[34,41,44] Panaxadiol ginsenosides (particularly Rb2), but not total saponins, have also been found to up-regulate the transcription of other known antioxidant enzymes (superoxide dismutase and catalase) by two- to three-fold in human hepatoma cells.[45] Rb3, Rb1, and Rc are antioxidants that, alone or in combination, show significant synergistic interaction with alpha-tocopherol (aTOC). With the exception of Rg1, the 20(S)-protopanaxatriols show synergistic antioxidant interaction with aTOC. All ginsenoside antioxidants have a sugar at position 6, and a pro-oxidant molecule results when glucose is not bound to position 20. Rg3, Rd, and Rh2 have pro-oxidative effects when used alone or in combination with aTOC.[42,43]

Induction of Apoptosis

Apoptosis can be induced by immune cells and cytotoxins, and by changes in homeostatic signals (Figure 3).[46] The mechanisms associated with changes in gene expression require caspase activation through two main pathways.[47] The first involves the interaction of a death receptor with its ligand, and the second depends on the participation of mitochondria involving pro- and anti-apoptotic members of the Bcl-2 family (Figures 4 and 5).[16]

Rb1 metabolites (Rh2, Compound K, and panaxydiol) have been shown to encourage apoptosis by inducing caspase-3 without any known activation of caspase-8.[48-50] Recently, however, Compound K was noted to initiate the caspase-8 model of apoptosis and has produced a link between caspase-3 and caspase-8 by an amplification loop perhaps initiated by cytochrome-c.[51] Interestingly, the loss of cytochrome-c from the mitochondrial membrane has been shown to be a function of pro-apoptotic Bcl-2 proteins,[52] although no affect on Bcl-2 expression has been found with Rh2 and Compound K.[50,53] A further conundrum is the ability of Rh2 to activate the caspase pathway in a Bcl-X_L-independent manner, suggesting additional apoptotic induction pathways available to ginsenosides.[53]

Other studies support the use of Rb1 metabolites for inducing programmed cell death. First, Compound K produces apoptosis in cells otherwise safeguarded from apoptosis by fibroblast growth factor over-expression.[54] Second, caspase-induced apoptosis is promoted by the additional ginsenoside actions of inducing cyclin-dependent kinases to depolarize the mitochondrial membrane (panaxydiol)[53,55] and by the concomitant production of ROS (Rh2).[53] Finally, these Rb1 metabolites have induced known promoters of

apoptosis, including the cleavage of poly-ADP ribose polymerase (PARP); the up-regulation of Bax, Bid, p53, p21, and p27 proteins; and the decreased expression of c-myc and cyclin D, E and A kinases. [48-51,55-59] (The inducing effects of *P. ginseng* in all these studies were abrogated by inhibitors verifying ginsenoside action.)

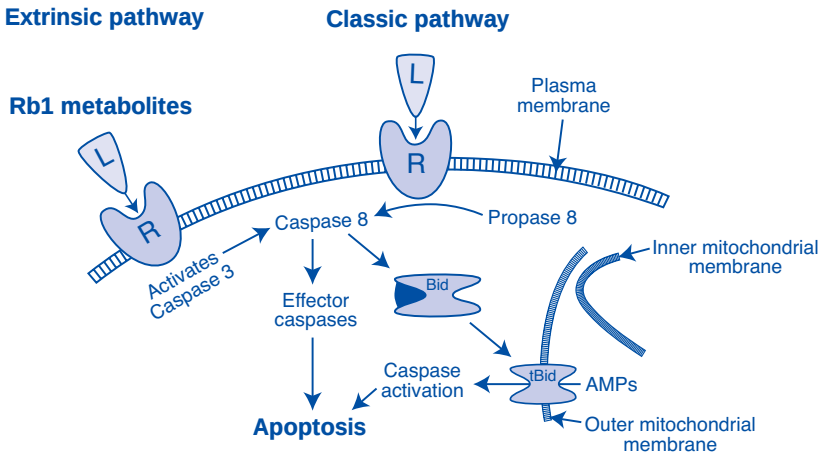
Inhibition of Proliferation

The proliferation phase, including tumor-cell migration, invasion, and metastasis, is modulated by neurotransmitters and chemokines (Figure 6).[17] The protopanaxadiol metabolites of *P. ginseng* have been shown to reduce catecholamine secretion through binding to nicotinic receptors and blocking sodium influx through the receptors.[2] Catecholamines have been noted as a chemo-attractant of breast carcinoma cells[59] and as an activator for the migration of colon carcinoma cells.[60] The therapeutic benefit of *P. ginseng* in neurotransmission warrants further investigation.

P. ginseng has also been noted to reduce lung metastasis in two highly metastatic tumor cell lines – colon 26-M3.1 and B16-BL6 melanoma; Rb2 inhibits their angiogenesis.[61] Rg3 inhibits the adhesion of tumor cells to extracellular matrix and basement membrane components[62,63] and, despite inhibiting metastasis, does not change the growth or vascularity of induced intestinal cancers.[64]

Rb1 and its metabolite (Compound K) have shown reduction in lung metastasis in mice injected with Lewis lung carcinoma. Compound K was found to be twice as effective as Rb1 and to have almost the same antimetastatic potential as 5-fluorouracil (5-FU) – a chemotherapeutic agent. Because of the potential toxicity of 5-FU, Compound K may provide promising long-term therapy, given its low toxicity – LD_{50} > 5g/kg.[65]

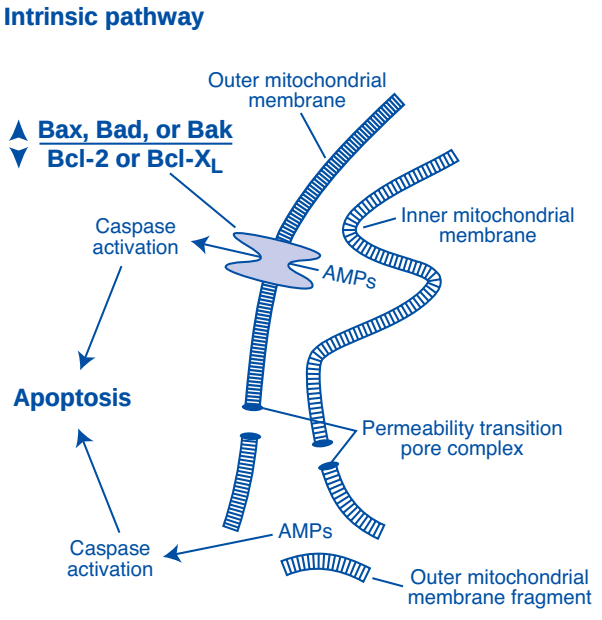
Figure 4. Regulation of the Apoptotic Pathways: The Extrinsic Pathway



Bid = proapoptotic Bcl-2 family member; tBid = truncated Bid; AMPs = proapoptotic mitochondrial proteins

From: Sun SY, Hail N Jr, Lotan R. Apoptosis as a novel target for cancer chemoprevention. *J Natl Cancer Inst* 2004;96(9):662-72.

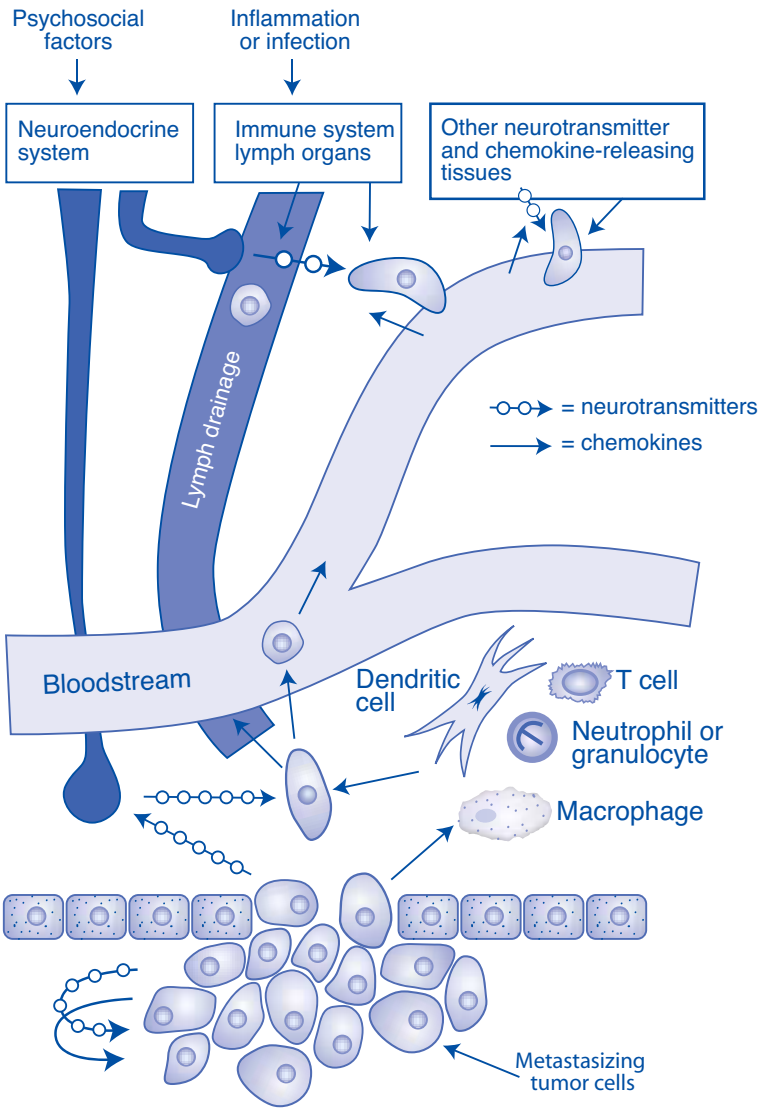
Figure 5. Regulation of the Apoptotic Pathways: The Intrinsic Pathway



AMPs = proapoptotic mitochondrial proteins

From: Sun SY, Hail N Jr, Lotan R. Apoptosis as a novel target for cancer chemoprevention. *J Natl Cancer Inst* 2004;96(9):662-72.

Figure 6. Neurotransmitters and Chemokines as Regulators of Metastasis



Adapted from: Entschladen F, Drell TL 4th, Lang K, Joseph J, Zaenker KS. Tumour-cell migration, invasion, and metastasis: navigation by neurotransmitters. *Lancet Oncol* 2004 Apr;5(4):254-258.

One study does note an increased metastatic potential of *P. ginseng*. In an experimental cell line, Rh2 was found to increase metastatic potential, perhaps through the inhibition of Cdk2 (a cyclin-dependent kinase) producing an apoptotic-resistant state. The same study of BALB/c3T3 cells showed Rh2 suppression of tumor growth in the initiation stage.[66]

Immunomodulation

No direct evidence confirms the cancer therapeutics of *P. ginseng* through immunomodulation. However, recognition of the concert of immune functions that incite apoptosis in cancerous cells is well known. It is understood that natural killer (NK) cells are pivotal in inhibiting tumor cell proliferation, and that the dynamic interplay of both cellular and humoral immunity is paramount to the containment of aberrant cell lines. In all these domains, *P. ginseng* has been studied and has demonstrated these actions with ginsenosides[67-71] and the polysaccharide fractions.[14,72-75]

The immunomodulating qualities of *P. ginseng* may also be associated with a dampening of glucocorticoid levels and its activity. Mixed outcomes have been reported involving ginsenosides' action as a functional ligand to glucocorticoid receptors.[76-79]Nonetheless, a recent rat study displays significant reduction in serum corticosterone levels after oral administration of whole ginseng root at a daily dose of 100 mg/kg body weight.[80] In addition, red ginseng has reduced immune suppression through lowering elevated corticosterone, although the mechanism is unknown.[78]

Applications of Ginseng or its Constituents in Specific Cancer Types

Colon Cancer

In a dose-dependent manner (2.5 and 5.0 mg/kg), a rat study using Rg3 found reduction in metastasis and tumor number as well as increased body weight.[64] Red ginseng, also in a dose-dependent manner (0.5 and 2.0 mg/kg), significantly

reduced dysplastic crypts, although initiation phase inhibition was weak, limiting a prophylactic effect.[81,82]

Gastric Cancer

Red ginseng was found effective in patients with stage III gastric cancer for improving both post-operative immunity and survival. Increased CD3 and CD4 activity was reported with a five-year survival for *P. ginseng* patients markedly higher than control (68.2% versus 33.3%). Reported dose was 4.5 g/day for the first six months after surgery.[83] Inhibitory effects have also been found in cell-line cultures.[84-86]

Hepatic Cancer

Red ginseng (3.78 g/kg/wk) was shown to act as a highly significant preventative to induced liver cancer. In a rat study, when taken for 15 weeks prior to diethylnitrosamine exposure, only 14.3 percent of the rats had liver morphological changes indicative of cancer, while the control group tallied 100-percent induction. *P. ginseng* acts to decrease the speed of tumor development and protect the ultrastructure of hepatocytes.[87] *P. ginseng* metabolites (Rg3, Rg5, Rk1, Rs5, and Rs4) have a 50-percent growth inhibition concentration in hepatoma cells – significantly lower than cisplatin (CDDP).[88] Other positive studies from 1978-2004 are noted with hepatoma cell lines.[19,20,45,48,49,51,55,57]

Kidney Cancer

The proliferation of renal cell carcinoma is reduced with red ginseng via a decrease in c-fos and c-jun gene expression. Only partial inhibition was produced with use of -diol or -triol fractions independently.[89]

Leukemia

In the human promyelocytic leukemia cells (HL-60) *P. ginseng* (fresh steamed) has been shown to scavenge ROS[44] and Compound K to induce apoptosis and inhibit proliferation.[50]

Melanoma

In mice, ginseng extracts and ginsenosides both significantly inhibited lung metastasis from melanoma.[90] Cell-line studies have shown control of differentiation (by Rh1 and Rh2),[21,22] inhibition of proliferation (by red ginseng),[8] inhibition of tumor angiogenesis and metastasis (by Rb2),[61] and most recently proliferation inhibition via up-regulation of p27 and down-regulation of c-Muc and cyclin D1 (by Compound K).[56]

Ovarian Cancer

Rh2 was found to inhibit ovarian tumor growth in mice by induction of apoptosis and increased NK-cell activity. Oral, but not intraperitoneal, treatment was found effective. The dose of 0.4-1.6 mg/kg was significant when given daily, but not weekly. The antitumor activity was similar to 4 mg/kg of CDDP, while also expressing a significant increase in survival.[91]

Prostate Cancer

Rg3 has displayed growth inhibitory activity as well as reduced biomarkers for prostate cancer (notably prostate specific antigen, androgen receptors, and 5 alpha-reductase). This study suggests induction of apoptosis through caspase-3 with the activated expression of cyclin-kinase inhibitors, p21 and p27.[92]

Pulmonary Cancer

Compound K has been shown to treat CDDP-resistant pulmonary cancer, with only a 20.3 microM concentration needed to inhibit cell proliferation by 50 percent (CDDP 60.8 microM).[86] Ginsenosides have shown significant effect in induced lung cancers.[24-26,65,93,94] A polysaccharide fraction has also shown dose-dependent inhibition in mouse lung tumor incidence.[72]

Other Cancer-related Uses

Ultraviolet Radiation Protection

Prepared under high heat, red ginseng extract has protected DNA from UV-induced fragmentation – the heralding of apoptosis.[44] *P. ginseng* has also been shown to protect different cell

lines from ultraviolet radiation by increasing the rate of DNA repair[31] and by impeding apoptosis by maintaining constant levels of anti-apoptotic Bcl-2.[95]

Radiation Therapy Adjunct

In one study, water-extracted polysaccharides were injected into mice before treatment with ionizing radiation. Mice pretreated with 100 mg/kg survived a radiation dose ($LD_{50/30}$) 45-percent more intense than control (10.93 Gy vs. 7.54 Gy). Cytokines, including interleukins (IL-1, IL-6, IL-12) and interferon-gamma, required for hematopoietic recovery were induced with enhanced T-helper 1 function. The pretreated cells had a significantly increased number of bone marrow, spleen cells, granulocyte-macrophage colony-forming cells, and circulating neutrophils.[96]

Chemotherapy Adjunct

P. ginseng has been shown to improve the delivery and action of chemotherapeutic agents in addition to curtailing negative effects. Rc and Rd are capable of significantly reversing multidrug-resistant lymphoma cells by decreasing the expression of the mdr1 glycoprotein gene – effectively inhibiting the efflux pump function on tumor cells.[69]

Rg1 and Re have been shown to reverse P-glycoprotein (Pgp) mediated multidrug resistance, thereby increasing the intracellular accumulation of drugs. Furthermore, ginsenosides decrease the levels of Pgp affording possible long-term treatment where verapamil and cyclosporin A increase Pgp levels at maximum non-cytotoxic concentrations.[97]

Panaxytriol was found to promote cellular accumulation of mitomycin C into gastric carcinoma and enhance its cytotoxicity.[85] In NIH3T3 mouse fibroblast cells, a mixture of -diol and -triol ginsenosides potentiated the apoptotic cell death of the alkylating agent methyl methanesulfonate.[58] In addition, Rg1 was found to restore cyclophosphamide-impaired cellular and humoral responses through activation of macrophage IL-1 production.[98]

Ginsenosides at 2-20 mcg/mL have increased tumor antigen expression,[69] and associated antigen-guided cancer therapies may gain insight from studies concerning the concurrent use of *P. ginseng* with immunization outcomes. Rg1 given before general immunizations resulted in increased titers of circulating antibodies, increased activity of NK cells, and increased number of T-helper cells.[98] Furthermore, daily administration of 100 mg of four-percent standardized ginsenosides to patients for 12 weeks enhanced the efficacy of polyvalent influenza vaccine.[67]

End of Life

Morphine is often used as a palliative in metastatic cancer. *P. ginseng* exerts protective effects against morphine-induced depression of B-cell and T-cell functions.[78] Rf potentiates a kappa opioid-induced analgesia and demonstrates the ability to inhibit the tolerance to this analgesia in a dose-dependent manner.[99] This may lead to reduced morphine dosing and a subsequent increase in social functioning.

Toxicity and Adverse Effects

P. ginseng is unlikely to cause pharmacokinetic interactions. Ginseng does not significantly induce cytochrome P450 (CYP) activity,[100] has no effect on warfarin pharmacokinetics,[101] and the attainment of serum concentrations capable of modulating CYP activity *in vivo* seems unlikely after oral administration.[102] A 30-percent greater ethanol clearance, however, may imply CYP induction after alcohol dehydrogenase pathway exhaustion.[103]

Data from clinical trials suggest the incidence of adverse events with ginseng is similar to placebo. Case reports reveal the following correlated side effects with *P. ginseng* intake: cerebral arteritis (1), mastalgia (6), postmenopausal vaginal bleeding (2), metrorrhagia (1), gynaecomastia (1), increased mania in depressive illness (1), hypertension (2), and eye symptoms associated with mydriasis and disturbed accommodation (2).[104]

Intake over 15 g/day resulted in depersonalization and confusion in four patients, while inducing depression in higher doses. A “ginseng

abuse syndrome" has also been reported with doses up to 15 g/day, averaging 3 g/day, with concomitant use of caffeinated beverages. Symptoms were characterized by hypertension coupled with nervousness, sleeplessness, skin eruptions, and morning diarrhea in 14 patients. The syndrome was reported to reappear throughout the first year of the trial, but was found to be rare at 18 and 24 months.[105]

Ginseng standardized to four-percent ginsenosides has been found to increase the lumenal clearance of albendazole sulfoxide, an antihelminthic drug, speaking to both the need for concern with lowering serum levels of the benzimidazole-containing drugs and the possible adjunctive delivery of therapeutic agents to disturbances of the bowel.[106]

Studies with *P. ginseng* are often of short duration and the majority of trials include a relatively small number of patients, thus reducing potential reports of rare and delayed adverse events. Conversely, three case control studies in Korea with more than 10,000 patients provided no information regarding adverse effects.[107-109] Reports of toxicity are rare in Germany and other European countries in which ginseng is medically prescribed. Indeed, both the World Health Organization and the Commission E conclude that, in recommended doses (1-2 g of the crude drug or 200-600 mg of standardized extracts – calculated to 4-7 percent ginsenosides), there are no known side effects of *P. ginseng*.[13]

Conclusion

Cancer is both a systemic concern and a specific disease. The goal of cancer chemoprevention is to inhibit the induction and suppress the progression of preneoplastic lesions to invasive cancer. *P. ginseng's* protective effects from toxic insult are well documented and speak well to prophylactic use, especially in patients at high risk for liver cancer. The ability to decrease inflammation and increase antioxidant activity sustains ginseng's role as an antitumor agent. Induction of apoptosis is an area where the genetic mechanisms of ginseng are becoming best understood. Unfortunately, the inhibition of proliferation has had limited success, with future therapeutics on the horizon via neurotransmitter modulation. Therefore, given the short interval of initiation and progression (which are generally considered irreversible), the promotion phase may provide the best target for cancer prevention.

Much anecdotal evidence is claimed, but there is no conclusive proof *P. ginseng* cures any type of cancer. Nonetheless, evidence points to ginseng's ability to limit and slow growth as well as to enhance the ability of the immune system and tumor cells to overcome chemotolerance and incite apoptosis. The ability of *P. ginseng* to increase the effectiveness of other chemotherapeutic agents, to act synergistically, and to help lower doses and therefore adverse side effects, is increasingly documented. Ginseng and its constituents exhibit key properties that allow precancerous cells to be limited to the promotion phase or to be destroyed altogether.

Despite the lack of Western-style scientific experimentation, the use of *P. ginseng* for cancer is well accepted in China. This herbal therapeutic agent has only gained scientific attention in the West since 1972 when U.S. President Nixon visited China and successfully opened relations. Nonetheless as *P. ginseng* experimentation continues, its recognized potential in cancer therapeutics continues to grow.

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