

SAFETY AND EFFICACY OF *PANAX GINSENG* DURING PREGNANCY AND LACTATION

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ABSTRACT

Background

There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and the safety of herbs used by women during pregnancy and lactation. This is one article in a series that systematically reviews the evidence for herbs commonly used during pregnancy and lactation.

Objectives

To systematically review the literature for evidence on the use, safety and pharmacology of *Panax ginseng*, focusing on issues pertaining to pregnancy and lactation.

Methods

We searched 7 electronic databases and compiled data according to the grade of evidence that was found.

Results

Based on strong scientific evidence from a cohort study, *Panax ginseng* was not associated with adverse effects when used during pregnancy. *Panax ginseng* was misrepresented in the literature as causing androgenization, when, in fact, the case reported was due to an adulterant. There is *in vitro* evidence of teratogenicity with exposure to ginsenosides; however, this evidence is derived from animal embryos and is based on exposure to isolated ginsenosides at much higher levels than achievable through normal consumption in humans. There is also conflicting evidence as to whether or not *Panax ginseng* has estrogenic properties. In lactation, there are no human studies on the safety of *Panax ginseng*, only *in vitro* evidence based on three animal studies reporting minimal risk.

Conclusions

Panax ginseng should be consumed with caution during pregnancy, especially during the first trimester, and during lactation.

Key words: *Panax ginseng*, *asian ginseng*, *ginseng*, *pregnancy*, *lactation*, *breastfeeding*, *systematic review*

There are five main species of ginseng: American, Chinese, Korean, Japanese and Siberian (or Russian) and it is important to be able to distinguish between them. The commercially available product 'ginseng' usually refers to the dried root of *Panax ginseng*, commonly known as

Korean or Asian ginseng. Preparations of *P. ginseng* include the steam-dried root that is called 'red ginseng', and the air-dried root that is called 'white ginseng'.¹ Fresh ginseng extract is also consumed, but is not generally the preparation available commercially.² *Panax ginseng* is a

popular herbal remedy that has been in use for thousands of years. It has been an important part of the pharmacopoeia of Traditional Chinese Medicine and is classified as an adaptogen that is thought to increase the body's overall resistance to stress and infection.³ This herb has a wide base of application and is considered the most popular herbal medicine worldwide.⁴ It has been used to treat a variety of disorders including: anaemia, insomnia, dyspnea, memory impairment, confusion, decreased libido, chronic fatigue, angina, diabetes mellitus and herpes simplex type-II infections.^{2,5,6}

P. ginseng is not considered an herb specific to women's health issues. However, its broad base of popularity will invariably involve its usage by women of reproductive age and women who may be potentially pregnant. We conducted a systematic review of the literature to assess issues of efficacy, and potential safety for women who are pregnant, planning to become pregnant or those who are breast-feeding.

Synonyms/Common Names/Related Substances

Asian ginseng, Asiatic ginseng, Chinese ginseng, ginseng, ginseng asiatique, *Ginseng radix*, ginseng root, guigai, hong shen, Japanese ginseng, jen-shen, jinsao, jintsam, insam, Korean ginseng, Korean *panax ginseng*, Korean red ginseng, ninjin, Oriental ginseng, *Panax ginseng*, *Radix ginseng rubra*, red ginseng, ren shen, renshen, renxian, sang, seng, sheng shai shen, white ginseng⁷

Constituents

Triterpenoid Saponins: ginsenosides (Rg1, Rb1) Polyacetylenic constituents⁸: panaxynol, panaxydol, panaxytriol, Panaxagin⁹, Essential oil¹⁰, Phytosterol¹⁰, Pectin¹¹, B vitamins¹¹, Flavonoids¹¹

Part Used

Root and rhizomes⁷

METHODS

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all the relevant scientific medical literature that provided information as to the safety, efficacy and pharmacology of *Panax ginseng* in pregnancy and

lactation. Our search included the following databases from inception to June 2006: AMED, CINAHL, Cochrane CENTRAL, Cochrane Library, MedLine, Natural Database and Natural Standard. The common and the Latin names of the herb were used as the key words along with "pregnancy", "lactation" and "breastfeeding". In addition, we searched the Complete German Commission E Monographs by the American Botanical Council.

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then abstracted and compiled in the final report. The grade of evidence for indications was evaluated as displayed in Table 1. Evidence of harm was rated as displayed in Table 2.

RESULTS

Indications for Use

	Evidence Grade
Erectile dysfunction ¹²	B1
Premature ejaculation ¹³	B1
Type II diabetes ¹⁴	B1
Influenza and the common cold ¹⁵	B1
Memory improvement ¹⁶⁻¹⁸	B2
Improved cognitive function ¹⁹⁻²²	B2
Enhanced physical function ²³	B2
Chronic bronchitis (with antibiotics) ²⁴	C
Cancer prevention ^{25,26}	C
Parkinson's disease ²⁷	E

Use and Safety during Pregnancy

	Level of evidence for potential harm
Non-estrogenic ²⁸	1
Treatment of intrauterine growth retardation ²⁹	2
Estrogenic ³⁰	3b
No evidence to support androgenization ^{31,32}	3b
Protection of neonatal brain against ethanol damage ³³	4
Teratogenicity ³⁴⁻³⁷	4
Activates DNA polymerase delta in placenta ³⁸	4
Traditionally used during pregnancy ³⁹	4

A randomized controlled trial of 384 women receiving either ginseng extract or placebo for 16 weeks, showed that the beneficial effects in the treatment of menopause are most likely not mediated by hormone replacement-like effects, as physiological parameters such as FSH and estradiol levels, endometrial thickness, maturity index and vaginal pH were not affected by the treatment.²⁸

On the other hand, there are case reports and animal studies indicating potential estrogenic activity due to ginseng. Evidence includes postmenopausal vaginal bleeding, increased serum ceruloplasmin oxidase activity and phytoestrogenic actions of ginsenoside Rb1.⁴⁰⁻⁴⁶ A review article on the potential value of plants as sources of anti-fertility agents also reported that Korean ginseng has estrogenic activity.³⁰

Zhang et al. (1994) conducted a comparison study on pregnant women with intrauterine growth retardation (IUGR).²⁹ One group of women received ginseng, while the other group was nutritionally treated as controls.²⁹ The height of fundus, fetal biparietal diameter, urinary estrogens/creatinine, serum human placental lactogen and neonatal weights approached normal pregnancy values.²⁹ The authors did not report any adverse effects associated with ginseng supplementation.²⁹

A case was reported of a 30-year-old woman who gave birth to a full-term baby boy with signs of androgenization following ingestion of “ginseng” during her pregnancy.³² After further investigation, the herbal preparation used by the mother appeared to be adulterated by the herb silk vine (*Periploca sepium*).³¹

Okamura et al. (1994) reported that ginseng extract prevented an ethanol-induced reduction of neonatal brain weight in rats.³³ The ginseng saponins, including ginsenosides Rg1, Rb2, Rd, Rf and Re, were shown to stimulate a potent recovery of cerebellum growth.³³

Chan et al. have demonstrated that ginsenosides Rb1, Rc and Re exert direct teratogenic effects on rat embryos.^{34,37} A separate group of investigators also found embryotoxicity when rat and mice whole embryos cultures were exposed to high concentrations of the two ginsenosides, Rg1 and Rb1.^{35,36} Ginsenosides from *Panax ginseng* were found to activate DNA polymerase delta in bovine placenta.³⁸

Researchers conducted a review of the herbs used during pregnancy in Singapore.³⁹ *Panax ginseng* was used in various combinations and in various amounts in herbal prescriptions during pregnancy.³⁹ The researchers could not confirm that the claims made by Chinese herbalists on the efficacy of *Panax ginseng* in pregnancy were real or not.³⁹ They concluded that there is no specific effect on pregnant women, but that it does not exclude the possibility of a beneficial psychosomatic effect.³⁹ The researchers also noted that the active principles can cross the placenta and reach the fetus.³⁹ The authors did not discuss if *Panax ginseng* was safe or contraindicated during pregnancy.³⁹

Use and Safety during Lactation

	Level of evidence for potential harm
Minimal risk ^{47,49}	4

Cows with subclinical mastitis caused by *Staphylococcus aureus* were given subcutaneous injections of an extract of the *Panax ginseng* root.⁴⁷ Based on blood leukocyte measurements, ginseng treatment was found to activate the innate immunity of cows and contribute to the cow's recovery from mastitis.⁴⁷ The authors did not report any adverse effects associated with the use of *Panax ginseng* during lactation.⁴⁷ Two other studies by the same authors, conducted in lactating cows, found similar results where *Panax ginseng* increased leukocyte activity and no adverse effects were reported.^{48,49}

Toxicity and Adverse Effects

Very low incidence of toxicity has been observed in ginseng clinical trials using well-characterized preparations.⁵⁰ When used inappropriately, *Panax ginseng* has been noted to cause hypertension, diarrhea, sleeplessness, mastalgia, eruptions and vaginal bleeding.¹ Siegel has coined a condition called “ginseng abuse syndrome”, in reference to the long-term effects of ginseng use. This ‘syndrome’ is characterized by hypertension, nervousness, sleeplessness, skin rash, diarrhea, confusion, depression or depersonalization.⁵¹

Pharmacology

It is clear that *Panax ginseng* is pharmacologically active. While it is uncertain to what extent isolated constituents are biologically active, the ginseng saponins (or ginsenosides) are considered to be responsible for a majority of this species' biological activity.⁵² Ginsenosides are unique to *Panax ginseng* and over 30 of these compounds have been identified.¹ Some of the known pharmacological effects are detailed in Table 3, and attest to the wide range of potential therapeutic applicability of this incredibly popular and seemingly potent herbal medicine.

Drug Interactions

There is some evidence of potential interactions between ginseng and prescription drugs; however, most of the evidence is derived from preclinical assays. Confirmation from pharmacokinetic studies should be conducted to establish true interactions. Current evidence requires that *Panax ginseng* be used with caution in conjunction with the following agents:

- Anitcoagulent drugs^{53,54}
- Antidiabetic drugs⁵⁵
- Antipsychotic drugs⁵⁶
- Caffeine⁵⁷
- Furosemide⁵⁸
- Immunosuppressants²⁶
- Insulin⁵⁷
- Monoamine Oxidase Inhibitors^{59,60}
- Stimulant Drugs⁶¹
- Warfarin (Coumadin)^{53,54,62}

DISCUSSION

Panax ginseng is frequently used as a general tonic or "adaptogen" to fight stress, and possibly to enhance physical and mental performance. This herb is not specifically used during pregnancy and lactation in the same way that ginger might be used to treat nausea and vomiting, or how horse chestnut seed extract might be used to treat varicose veins.^{63,64} However, the fact that it is one of the most commonly used herbs worldwide, inevitably women will end up taking the herb during pregnancy or while breastfeeding. As such, it is critical that both women and clinicians be

aware of the possible risks attendant to such usage and to be able to plan and advise accordingly.

There is no high-grade evidence demonstrating that *P. ginseng* is unsafe during pregnancy and lactation. Observations during a cohort, and from traditional use, have not uncovered any adverse events from ginseng with respect to pregnancy and lactation. A single case report was found in the literature that reported on a potential link between *P. ginseng* use by a pregnant woman and the death and androgenization of her fetus.³¹ It was determined that the ginseng-containing-product was adulterated, however, and as such, we cannot infer that ginseng was the causative agent. In addition, this is an isolated case and the anecdotal nature of the evidence does not provide anything beyond speculation. Of somewhat greater concern, however, are the repeated findings of teratogenicity in mice and rats when exposed to ginsenosides. Again, this evidence must be interpreted with caution, as it is derived from animal embryos and is based on exposure to isolated ginsenosides at much higher levels than achievable through normal consumption in humans. Evidence regarding phytoestrogenic activity of *P. ginseng* is conflicting; some concern may be justified regarding this possibility, especially with respect to exposure during early fetal development.

Our study is limited primarily by the lack of evidence available. Given the vulnerabilities of a developing fetus and newborn child, and the fact that their metabolism can vary substantially from the adult, extreme caution is required in making recommendations for women of child bearing age. The totality of the evidence that we analysed in our systematic review indicates that *Panax ginseng* may well be safe for consumption during pregnancy; however, to ensure safety to the developing fetus, consumption of this herb is best avoided, especially during the first trimester.

No human evidence could be found regarding the safety of consuming *Panax ginseng* while breastfeeding. Nonetheless, there is *in vitro* evidence based on three animal studies that *Panax ginseng* was of minimal risk when consumed by lactating cows. Research is necessary to determine if ginsenosides and other potentially active compounds are carried in the human breast milk, and also how this might affect a newborn child.

There is evidence to support the use of *Panax ginseng* in the treatment of male sexual dysfunction; care of type II diabetics; amelioration of symptoms from influenza and the common cold and to enhance cognitive and physical function; however, more research is necessary to establish its use in these areas as well as to establish safety during pregnancy and lactation.

TABLE 1 Levels of Evidence for Efficacy

GRADE	LEVEL OF EVIDENCE
A	VERY STRONG SCIENTIFIC EVIDENCE Statistically significant evidence of benefit from one or more systematic reviews/ meta-analysis.
B1	STRONG SCIENTIFIC EVIDENCE Statistically significant evidence of benefit from one or more properly conducted random control trials (RCTs).
B2	GOOD SCIENTIFIC EVIDENCE Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size OR have discrepancies in their methodologies.
C	WEAK SCIENTIFIC EVIDENCE Statistically significant evidence of benefit from one or more cohort studies OR case control studies.
D	VERY WEAK SCIENTIFIC EVIDENCE Evidence from case series OR case reports.
E	INDIRECT EVIDENCE Expert opinion OR laboratory studies.
F	HISTORICAL OR TRADITIONAL EVIDENCE Historical or traditional use by medical professionals, herbalists, scientists or aboriginal groups.

TABLE 2 Levels of Evidence for Harm

LEVEL	EVIDENCE
1	STRONG SCIENTIFIC EVIDENCE Statistically significant evidence from one or more systematic reviews or RCTs.
2	ACCEPTABLE SCIENTIFIC EVIDENCE Statistically significant evidence from one or more well designed cohort studies OR case control studies.
3a	WEAK SCIENTIFIC EVIDENCE Evidence from one or more case series.
3b	VERY WEAK SCIENTIFIC EVIDENCE Evidence based on case reports.
4	INDIRECT SCIENTIFIC EVIDENCE Evidence based on scientific studies conducted on animals, insects or microorganisms OR laboratory studies on human cells.
5	THEORETICAL EVIDENCE Evidence based on scientific theory OR expert opinion.
6	UNKNOWN No available information.

TABLE 3 Pharmacological Actions Attributable to *Panax Ginseng*

SYSTEM	PHARMACOLOGICAL ACTION
Adrenal	<ul style="list-style-type: none"> • Ginsenosides increase serum cortisol levels, stimulate adrenal function and in women, increase dehydroepiandrosterone sulfate (DHEA-S)⁶⁵⁻⁶⁸
Cardiovascular	<ul style="list-style-type: none"> • Ginsenoside Rb1 may lowers blood pressure and acts as a CNS depressant¹¹ • Ginsenosides interfere with platelet aggregation and coagulation⁴⁷ • <i>Panax ginseng</i> may lower cholesterol and triglycerides¹⁸
Antiinflammatory and antiinfective	<ul style="list-style-type: none"> • Ginsenosides have analgesic and anti-inflammatory effects¹⁸ • <i>Panax ginseng</i> has shown inhibitory activity on <i>Helicobacter pylori</i>⁶⁹ • <i>Panax ginseng</i> promotes the growth of normal intestinal flora while inhibiting Clostridial species⁷⁰ • The protein isolate panaxagin may have antiviral and antifungal activity where it appears to inhibit HIV reverse transcriptase and ribosomal activity of some fungi⁹
Neurocognitive	<ul style="list-style-type: none"> • Ginsenosides potentiate nerve growth factor and may have a neuroprotective effect through nicotinic activity^{11,71} • <i>Panax ginseng</i> increases penile vibratory threshold and reduces the amplitude of penile somatosensory evoked potentials¹³
Pulmonary	<ul style="list-style-type: none"> • Ginsenosides have anti-asthmatic effects through the relaxation of human bronchial smooth muscle by stimulating the release of nitrous oxide from airway epithelium⁷²
Endocrine system	<ul style="list-style-type: none"> • <i>Panax ginseng</i> may prevent insulin resistance and change gene expression in Type II diabetes⁷³ • Some studies report that <i>P. ginseng</i> has phytoestrogenic properties⁴⁰⁻⁴⁶

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