REVIEW ARTICLE

Drug Safety 2002; 25 (5): 323-344
0114-5916/02/0005-0323/$25.00/0

Panax ginseng
A Systematic Review of Adverse Effects and Drug Interactions

Joanna Thompson Coon and *Edzard Ernst*

Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, Exeter, United Kingdom

Contents

Abstract

Panax ginseng C.A.Meyer is a perennial herb native to Korea and China and has been used as an herbal remedy in eastern Asia for thousands of years. Modern therapeutic claims refer to vitality, immune function, cancer, cardiovascular diseases, improvement of cognitive and physical performance and sexual function. A recent systematic review of randomised controlled trials found that the efficacy of ginseng root extract could not be established beyond doubt for any of these

indications. In order to obtain a balanced assessment of the therapeutic value of *P. ginseng* it is also necessary to consider the safety profile. In view of the extremely widespread use of *P. ginseng* it seems important to ask whether this herbal medicine involves health risks for the consumer. This review was conducted as a systematic attempt to document and evaluate all the available safety data on *P. ginseng* root extracts.

Systematic searches were performed in five electronic databases and the reference lists of all papers located were checked for further relevant publications. All articles containing original data on adverse events and drug interactions with *P. ginseng* were included. Information was also requested from 12 manufacturers of ginseng preparations, the spontaneous reporting schemes of the WHO and national drug safety bodies. No language restrictions were imposed.

Data from clinical trials suggest that the incidence of adverse events with ginseng monopreparations is similar to that with placebo. The most commonly experienced adverse events are headache, sleep and gastrointestinal disorders. The possibility of more serious adverse events is indicated in isolated case reports and data from spontaneous reporting schemes; however, causality is often difficult to determine from the evidence provided. Combination products containing ginseng as one of several constituents have been associated with serious adverse events and even fatalities. Interpretation of these cases is difficult as ingredients other than *P. ginseng* may have caused the problems. Possible drug interactions have been reported between *P. ginseng* and warfarin, phenelzine and alcohol. Collectively, these data suggest that *P. ginseng* monopreparations are rarely associated with adverse events or drug interactions. The ones that are documented are usually mild and transient. Combined preparations are more often associated with such events but causal attribution is usually not possible.

Panax ginseng C.A.Meyer is a perennial herb native to Korea and China and has been used as an herbal remedy in eastern Asia for thousands of years. It was first described in the UK in a letter from Father Jartoux to the Procurator General of the Missions of India and China dated Peking April 12, 1711.[1] The name *Panax* derives from the Greek words pan (all) and akos (healing), all-healing or panacea whilst ginseng means 'man-root' due to the shape of the root, creating a belief that it can benefit all aspects of the human body. All parts of the plant contain pharmacologically active constituents; however, it is the root that is most highly regarded, making ginseng one of the most popular and expensive herbs in the world. *P. ginseng* was the second highest selling herbal supplement in the US in 2000 with gross retail sales of $US62 million.[2] *P. ginseng* is available in a wide range of forms and preparations (e.g. fresh root, alcoholic extracts, capsules, teas, cigarettes), both alone and in combination with a wide range of other ingredients. It appears in the Pharmacopoeias of several countries including Japan, China, Germany, France, Austria and the UK.[3-8] Traditionally it has been used to restore and enhance normal well-being and is known as an 'adaptogenic'. Modern therapeutic claims refer to vitality, immune function, cancer, cardiovascular diseases, improvement of cognitive and physical performance and sexual function.[9] A recent systematic review of randomised controlled trials found that the efficacy of ginseng root extract could not be established beyond doubt for any of these indications.[10] In order to obtain a balanced assessment of the therapeutic value of *P. ginseng*

it is also necessary to consider the safety profile. In view of the extremely widespread use of *P. ginseng* it seems important to ask whether this herbal medicine involves health risks for the consumer. This review was conducted as a systematic attempt to document and evaluate all the available safety data on *P. ginseng* root extracts.

1. Literature Retrieval and Assessment

Systematic literature searches were conducted in the following electronic databases to locate papers with information relating to the safety of *P. ginseng* in humans: Medline (via Pubmed), Embase, Amed (Alternative and Allied Medicine Database, British Library Medical Information Centre), The Cochrane Library (Issue 2: 2001), and CISCOM (Research Council for Complementary Medicine, London, UK) (all from their inception to May 2001). The search terms used were: adverse event, adverse effect, tolerability, toxicity, safety, risk, adverse drug reaction, drug interaction, side effect, toxic effect, ginseng, *Panax ginseng*, Korean ginseng and Ginsana. No language restrictions were imposed. Further relevant papers were located by hand-searching the reference lists of all papers and departmental files. In addition, data were requested from the following spontaneous reporting schemes: the WHO (Uppsala Monitoring Centre), and the drug safety bodies of the UK [Medicines Control Agency (MCA)], US [Food and Drug Administration (FDA)] and Germany [Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)]. Twelve manufacturers/distributors of ginseng products (based in Europe, the US and Korea) identified from standard reference texts[8,11] and internet searches were contacted and asked to supply any safety information held on file.

All data from clinical trials, case reports, case series and epidemiology studies in which ingestion or application of *P. ginseng*, Korean/Chinese/Oriental/red ginseng or ginseng was described were included in the review. Papers that specified the use of Siberian or American ginseng were excluded. Both mono- and multicompound preparations were included but assessed in separate categories. All sources of information obtained were read by one reviewer (JTC) and checked by the second author (EE). Data about adverse events associated with *P. ginseng* were extracted according to predefined criteria (patient population, preparation and dose, treatment duration, number and type of adverse events reported). No formal assessment was made of the validity of the data and no statistical analyses were performed.

2. Evidence from Clinical Trials

One hundred and forty-six clinical trials were located.[12-156] Of these, 82 reported the effects of ginseng (described as *P. ginseng*, Korean/Chinese/Oriental/red ginseng or ginseng) alone[12-93] whilst 64 reported the effects of ginseng in a multipreparation.[17,94-156]

2.1 Ginseng Monopreparations

Forty-eight studies were placebo controlled[12-59] (tables I and II), 14 compared the effects of ginseng with that of other compounds[60-73] (table III) and 20 studies had no control group[74-93] (table IV). Due to the wide-range of potential uses of ginseng, study populations included healthy volunteers (29 studies), athletes (13), the elderly (5), patients with erectile dysfunction (3), postmenopausal women (6), patients with essential hypertension (5), with respiratory diseases (3) and with hepatitis (3). Subjects received ginseng for 2 to 3 months in a substantial portion of studies (31 of 82), although the longest was 2 years in duration[17] and there were five studies in which ginseng was administered as a single dose.[24,38,46,56,90] In 25 studies, a standardised extract of *P. ginseng* (G115®[1] or Ginsana®, Pharmaton, SA, Lugano, Switzerland) which contains 4% ginsenosides was used, at a daily dose of 200mg.[12-16,25-33,36-38,60-62,64,74,75,78,79]

Twenty-six studies used Korean red ginseng powder at doses of between one and 11.25g/day,[18-23,44-47,49,50,53,68,69,71,73,80,81,86-91,93] two studies involved topical application of a ginseng ex-

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

tract containing 14% ginsenosides,[84,85] other studies used various forms of ginseng in daily dosages from 100mg to 6g, although the ginsenoside content was not known.

No information was provided regarding adverse events experienced during treatment with ginseng in 42 of the studies[25,29-35,37,38,40,42-44,46-48,50,51,54-56,59,60,62-66,68-71,73-75,79,81,86,87,90,92] and these are excluded from the tables. In five studies details of adverse events and patient withdrawals due to adverse events were provided but there was no indication as to which treatment the patients were re-

Table I. Placebo-controlled trials of ginseng monopreparations reporting adverse events (AEs)

Trial	n	Patient population	Preparation and daily dose	Treatment duration	AEs reported (no of patients)	
					ginseng group	placebo group
Wiklund et al.[12]	384	Post-menopausal women	G115® 200mg	16wk	7 SAEs and 124 AEs Most frequent: flu/cold (36), headache (10), gastrointestinal (13)	9 SAEs and 133 AEs Most frequent: flu/cold (35), headache (9), gastrointestinal (22)
Engels and Wirth[13]	36	Healthy men	G115® 200 and 400mg	8wk	Diarrhoea (3)	None reported
Gianoli and Riebenfeld[14]	83	Healthy volunteers	G115® 200mg	4mo	Nausea (1)	Nausea, dizziness, headache, stomach problems (5)
Scaglione et al.[15]	227	Healthy volunteers	G115® 200mg	12wk	Nausea, vomiting, anxiety, insomnia, epigastralgia (10)	Insomnia (1)
Allen et al.[16]	28	Healthy volunteers	G115® 200mg	3wk	Diarrhoea (2) – no treatment group specified	
Mulz et al.[17]	60	Patients with psycho-asthenic syndromes	G115® [dose not stated]	2y	Itching, eye burning (2)	Urticaria, itching, stomach pain, giddy feelings (4)
Han et al.[18]	34	Patients with hypertension	Red ginseng 4.5g root (300mg ginseng) ± other antihypertensive treatment	12wk	Upper abdominal discomfort (2) Also reported: diaphoresis, tiredness, constipation/dyspepsia (9) – no treatment group specified. Only 12 patients had ginseng alone	None reported
Cartwright[19]	22	Healthy volunteers	Korean ginseng 1000mg	30d	Stimulation, improved motor efficiency, increased appetite, diarrhoea, skin eruptions, sleeplessness, sleepiness (11)	Depression, improved motor efficiency, increased appetite sleeplessness (7)
Fulder et al.[20]	49	Elderly patients	Korean red ginseng 1.5g	10d	Diarrhoea (1) – no treatment group specified	
Kim et al.[21]	45	Women with postmenopausal osteoporosis	Red ginseng 50 mg/kg/d	12mo	Digestion problem (3)	Digestion problem (1)
Kim et al.[22]	35	Patients with psychogenic impotence	Korean red ginseng 2700mg	2mo	Digestive problem, diffuse itching (2)	None reported
Kim et al.[23]	64	Healthy volunteers	Red ginseng/white ginseng 11.25g	10d	Hyper- or hypothermia, hot flushes, diarrhoea, headache, insomnia, constipation, lip dryness, dizziness, loss of appetite – no treatment group specified	
Medvedev[24]	32	Healthy radio operators	Liquid ginseng root extract 2ml	Single dose	Lighter hand and increased appetite (number of patients not reported)	None reported

G115® = standardised ginseng extract, 4% ginsenosides (Ginsana®, Pharmaton SA, Lugano, Switzerland); **n** = number of study participants; **SAEs** = serious adverse events.

Table II. Placebo-controlled trials of ginseng monopreparations in which no adverse events were reported

Trial	n	Patient population	Preparation and daily dose	Treatment duration	Comment
Engels et al.[26]	19	Healthy females	G115® 200mg	8wk	None
Smith et al.[27]	19	Healthy females	G115® 200mg	8wk	None
D'Angelo et al.[28]	16	Healthy males	G115® 200mg	12wk	None
Scaglione et al.[36]	40	Patients with bronchitis	G115® 200mg	8wk	Adverse effects not specified; treatment well tolerated by all
Sorensen and Sonne[39]	112	Healthy volunteers	Ginseng extract 400mg	8-9wk	Six patients discontinued the study due to illness
Cherdrungsi and Rungroeng[41]	41	Healthy males	Standard ginseng extract 300mg	8wk	None
Kuwashima et al.[45]	30	Patients with unsettled complaints	Korean red ginseng powder 2.7g	6wk	None
Choi et al.[49]	90	Patients with erectile dysfunction	Korean red ginseng 1800mg	3mo	None
Mc Naughton et al.[52]	30	Athletes	Chinese ginseng 1g	6wk	None
Hallstrom et al.[53]	12	Healthy nurses	Korean ginseng 1200mg	3d	None
Zhao[57]	358	Middle to old aged volunteers	*Panax ginseng* 150mg	2mo	No vomiting and or long-term toxic effects seen in any patient
Sotaniemi et al.[58]	36	Patients with diabetes mellitus	Ginseng 100 or 200mg	8wk	None

G115® = standardised ginseng extract, 4% ginsenosides (Ginsana®, Pharmaton SA, Lugano, Switzerland); **n** = number of study participants.

ceiving when they were experienced.[16,18,20,23,60] In 20 studies no adverse events were observed in any patient,[26-28,41,45,49,52,53,57,61,67,76-78,80,82-84,88,91] whilst in the remaining 15 studies the following adverse events were reported: diarrhoea and gastrointestinal disorders, anxiety, sleep related problems, epigastralgia, flu/cold, headache, contact urticarial reaction, itching, eye burning, improved motor efficiency, feelings of well-being and stimulation, increased appetite, skin eruptions, lighter hand and skin feeling 'too tight'.

2.2 Ginseng Multipreparations

Thirty-two of the studies were placebo controlled[17,94-124] (tables V and VI), nine compared a ginseng combination product with other compounds[125-133] (table VII) and 23 studies had no control group[134-156] (table VIII). Patient popula-

Table III. Adverse events reported in comparative trials of ginseng monopreparations

Trial	n	Patient population	Preparation and daily dose/comparator drug	Treatment duration	Adverse events reported (no of patients)	
					ginseng group	comparator group
Scaglione et al.[60]	75	Patients with chronic bronchitis	G115® 200mg/antibacterial treatment	9d	Not specified Nine patients withdrew from the study spontaneously (no treatment group specified)	Not specified
Forgo and Kirchdorfer[61]	20	Sportsmen	G115® 200mg/G115s	9wk	None reported	None reported
Ding et al.[67]	45	Patients with heart failure	Red ginseng [dose not stated]/digoxin/both	15 pills	None reported	None reported in any group
Siegel[72]	18	Regular users of ginseng	Ginseng [various doses]/ginseng and other stimulants	12wk	Contact urticarial reaction (1) stimulation, wellbeing, nervousness	Allergic reactions (2), ginseng abuse syndrome (1), stimulation, wellbeing

G115® = standardised ginseng extract, 4% ginsenosides (Ginsana®, Pharmaton SA, Lugano, Switzerland); **G115s** = standardised ginseng extract, 7% ginsenosides (Pharmaton SA, Lugano, Switzerland); **n** = number of study participants.

Table IV. Adverse events reported in uncontrolled trials of ginseng mono-preparations

Trial	n	Patient population	Preparation and daily dose	Treatment duration	Adverse events reported (no of patients)
Lee et al.[76]	17	Patients with oligospermia	G115® 400mg	90d	None reported
Gross et al.[77]	15	Patients with chronic respiratory disease	G115® 400mg	3mo	None reported
Reinold[78]	49	Postmenopausal women	G115® 200mg	3mo	None reported
Tode et al.[80]	20	Postmenopausal women with and without climacteric symptoms	Korean red ginseng 6g	30d	None reported
Wyss et al.[82]	10	Male athletes	Pure ginseng extract 105mg	2d	None reported
Sohn et al.[83]	35	Patients with essential hypertension	Ginseng extract 1000mg	Up to 10wk	None reported
Gezzi et al.[84]	20	Healthy women	Epicutaneous extract of ginseng containing 14% ginsenosides	30d	None reported
Curri et al.[85]	20	Healthy women	Epicutaneous extract of ginseng containing 14% ginsenosides	30d	3 patients withdrew after 12-15 days due to skin feeling 'too tight'
Imamura and Kuwashima[88]	19	Patients with essential hypertension	Red ginseng powder 3g	12wk	None reported
Sung et al.[91]	17	Patients with hypertension	Korean red ginseng 4.5g	21-27mo	None reported
Kim et al.[93]	24	Patients with mild proteinaemia and hypertension	Red ginseng 900mg	2mo	Digestive problem (1)

G115® = standardised ginseng extract, 4% ginsenosides (Ginsana®, Pharmaton SA, Lugano, Switzerland); **n** = number of study participants.

tions studied included the elderly (10), healthy volunteers (16), patients with age-related mental impairment (9), and patients with premature ejaculation (5). The longest study was 2 years in duration[17] with almost half the studies being between 2 to 4 months length (29 of 64). In six studies patients received single doses of treatments.[113,115,124,146,147,150] Thirty-four studies involved a combination of vitamins, minerals and a standardised *P. ginseng* extract (G115®), Pharmaton® Capsules, Gericomplex® or Geriatric® Pharmaton, all manufactured by Pharmaton SA, Lugano, Switzerland).[17,94-106,108-110,116-119,123,125-128,130,131,134-139] The remaining trials tested a variety of compounds combined with ginseng including fenugreek, ginkgo and *Ophiopogon japonicus*.[107,111-115,120-122,124,129,132,133,140-156]

No information regarding adverse events was provided for 32 of the studies[101,103-109,112,113,115,127,129,132,133,135-138,140,143,144,147-156] and these are excluded from the tables. No patients reported any untoward effect of the ginseng preparation in 11 studies[17,95,96,100,102,110,111,114,130,131,139] and a general statement regarding lack of adverse events or patient withdrawals was provided in five studies.[94,97-99,128] In the remaining 16 studies the following adverse events were reported: sleep disorders, gastrointestinal symptoms, headache, depressive reaction, a swallowing problem, a cutaneous reaction, an increase in libido, unpleasant aftertaste, euphoria, nervousness, raised blood pressure, dizziness, increased micturition, pain around the xiphoid process, back pain, chest pain, loss of appetite, liver function problems, hot flushes, local burning sensation, mild local irritation and mild pain and delayed ejaculation (reported in trials of a cream for premature ejaculation). One study reported intolerance present in four patients from the ginseng group and in eight from the placebo group.[119] There was one death reported in a trial of 390 healthy volunteers, but the

investigators did not consider this to be related to the study drug.[117]

No apparent difference existed between the number of patients reporting an adverse event and the types of complaints reported between the ginseng and control groups. Information regarding causality was not provided in the majority of studies.

3. Evidence from Case Reports

Fifteen papers[157-171] describing a total of 27 case reports following ingestion of ginseng were identified. The reports referred to cerebral arteritis with explosive headache, nausea vomiting and chest tightness, mastalgia, gynaecomastia and vaginal bleeding, diuretic resistance, Stevens-Johnson syndrome, psychological disturbances, hypertension, shortness of breath, dizziness and inability to concentrate, agranulocytosis, and eye symptoms. In 22 of the reports no information was provided regarding the type or dose of ginseng ingested. A further five papers[172-176] outlined a total of 87 reports of pneumonitis, associated with the Japanese herbal preparation Sho-saiko-to, which contains *P. ginseng* as one of seven herbal ingredients.

3.1 Mastalgia, Vaginal Bleeding and Gynaecomastia

Six cases of women with mastalgia, two of postmenopausal vaginal bleeding and one of metror-

Table V. Placebo-controlled trials of ginseng combination preparations in which no adverse events were reported

Trial	n	Patient population	Preparation and daily dose	Treatment duration	Comment
Zuin et al.[94]	24	Elderly patients with chronic liver disease	G115®+ 80mg	12wk	No adverse effects reported that were definitely ascribable to ginseng extract
Dorling and Kirchdorfer[95]	23	Patients with poor mental and physical performance	G115®+ 80mg	12wk	None
Pieralsi et al.[96]	50	Healthy males	G115®+ 80mg	13wk	None
Neri et al.[97]	60	pts with age-associated memory impairment	G115®+ 80mg	9mo	No adverse effects requiring early withdrawal from the study were reported
Ussher et al.[98]	95	Healthy volunteers	G115®+ 80mg	2mo	No adverse effects reported in patients who withdrew from the study. No adverse effects were specified for those who completed the study
Curutchet Ragusin et al.[99]	98	Elderly patients	G115®+ 80mg for 3wk and 40 mg/d for 1 week	4wk	Excellent tolerability and lack of adverse events
Thommessen and Laake[100]	49	Elderly patients	G115®+ 80mg	8wk	None
Mulz et al.[17]	50	Patients with psycho-asthenic symptoms	G115®+ [dose not stated]	2y	None
Colombi[102]	40	Patients	G115®+ [dose not stated]	21d	None
Le Faou[110]	12	Athletes	G115®+ 80mg	6wk	None
Liao et al.[111]	32	Patients with angina	YHI 20ml in 250ml IV	2wk	None
Graubaum et al.[114]	18	Stressed, untrained volunteers	Ginseng [dose not stated], hawthorn, mixed pollen	40d	None

G115®+ = standardised ginseng extract, 4% ginsenosides plus vitamins and minerals (Pharmaton SA, Lugano, Switzerland); **n** = number of study participants; **YHI** = ginseng, *Astragalus* and *Angelica sinensis*.

rhagia and one case of gynaecomastia in a man have been described. A 70-year-old woman developed swollen, tender breasts with diffuse nodularity after taking ginseng powder regularly for 3 weeks. The symptoms resolved on cessation of the ginseng powder and returned following rechallenge on two occasions.[157] Five women aged between 25 to 40 years who had been taking ginseng for varying periods developed breast symptoms, particularly enlargement of the nipples, they also reported an increase in 'sexual responsiveness'.[158] A 72-year-old woman experienced vaginal bleeding after ingesting 200mg a day of a combination of ginseng, minerals and vitamins (Geriatric® Pharmaton),[159] and a 48-year-old woman was admitted to hospital with a 3-week his-

Table VI. Placebo-controlled trials of ginseng combination preparations reporting adverse events

Trial	n	Patient population	Preparation and daily dose	Treatment duration	Adverse events reported (no of patients)	
					ginseng group	placebo group
Le Gal et al.[116]	232	Patients with functional fatigue	G115®+ 80mg	42d	Nausea/vomiting sleep disorders, gastric disorders, bowel disorders (14)	Oedema of uvula, nausea/vomiting gastric disorders, headache (10)
					Two patients withdrew from ginseng group and three patients withdrew from placebo group	
Wiklund et al.[117]	390	Healthy volunteers	G115®+ 80mg	12wk	Gastric problems, sleeping problems, headache, illness, sleepiness, swallowing problem, death (11)	Gastric problems, nausea, sleeping problem, illness (9)
					In ginseng group, illness (1) and death (1) not believed to be drug related	
Garay Lillo[118]	60	Patients with involutional changes	G115®+ 80mg	8wk	Gastric discomfort (2)	Halitosis (2)
Hugonot et al.[119]	98	Elderly patients	G115®+ 80mg	2mo	Intolerance present (4)	Intolerance present (8)
					11 patients withdrew – no treatment group specified	
Kwiencinski et al.[120]	72	Patients with cerebro-vascular deficits	G115®+ and ginkgo 200mg	12wk	Headache and depressive reaction (1)	Worsening of irritable bowel syndrome, headache, paroxysmal atrial fibrillation, syncope, somnolence (5)
Choi et al.[121]	50	Patients with premature ejaculation	SS cream 0.05/0.10/0.15 and 0.20g prn		Local burning sensation (32 of 250 applications)	None reported
					No systemic adverse effects reported in either treatment group	
Wesnes et al.[122]	64	Patients with neurasthenia	G115®+ 50, 100 and 200mg and gingko	90d	Dizziness, somnolence abdominal pain, increased micturition, nausea (7)	Dizziness, increased micturition (2)
					All the above believed to be related to the treatment, others included headache, migraine, infections, vomiting and painful joints, 186 events in total	
Della Marchina and Renzi[123]	72	Patients with dementia	G115®+ 40mg	9 months	Mild gastralgia and nausea, meterorism and abdominal tension (4)	None reported
Choi et al.[124]	106	Patients with premature ejaculation	SS cream 0.20g	Single dose	Mild local burning and mild pain (98 of 530 applications)	Not specified
					No adverse event of sexual function and no systemic adverse effects reported in either treatment group	

G115®+ = standardised ginseng extract, 4% ginsenosides plus vitamins and minerals (Pharmaton SA, Lugano, Switzerland); **n** = number of study participants; **SS cream** = *Bufonis venenum*, *Angelicae gigantis radix*, *Cistanchis herba*, *Torilis semen*, *Ginseng radix alba* (white ginseng root), *Zanthoxyli fructos*, *Asiasaris radix*, *Caryophylli flos*, *Cinnamomi cortex*.

Table VII. Adverse events reported in comparative trials of ginseng combination preparations

Trial	n	Patient population	Preparation and daily dose/comparators	Treatment duration	Adverse events reported (no of patients)	
					ginseng group	comparator group
Marasco et al.[125]	625	Healthy volunteers	G115®+ 40mg/vitamins and minerals	12wk	Cutaneous reaction, headache, general discomfort, nausea, increase in libido, brucellosis (5)	Gastric irritation, specific dermatitis, changes in blood pressure (3)
					Two patients withdrew from the study due to an adverse event	
Mor[126]	91	Elderly patients	G115®+ 80mg/vitamins	5wk	Constipation, bloating, unpleasant aftertaste (27)	Constipation, bloating, unpleasant aftertaste (24)
					No significant difference between groups	
Poggi et al.[128]	60	Patients with senile involution	G115®+ 80mg and hydergine/ hydergine/vitamins and hydergine	30d	Local and systemic tolerance excellent	
Cascone[130]	50	Patients with age-related neurological changes	G115®+ 80mg with and without DMAE	30d	None reported	None reported
Alessandrini[131]	60	Elderly patients	G115®+ 80mg with and without ginseng	60d	None reported	None reported

DMAE = dimethylaminoethanol; **G115®+** = standardised ginseng extract, 4% ginsenosides plus vitamins and minerals (Pharmaton SA, Lugano, Switzerland); **n** = number of study participants.

tory of metrorrhagia after taking the equivalent of 120mg a day of ginseng in a similar product for 2 months (the recommended dose is 40 to 80 mg/day) [Pharmaton® Complex].[160] The woman was taking no other medication that might contain hormonal compounds, had no previous history of menstrual disorders and her symptoms resolved 4 days after discontinuing the ginseng preparation. A 44-year-old postmenopausal woman reported vaginal bleeding after using a ginseng face cream (Fang Fang ginseng face cream, Shanghai, China).[161] Application of the face cream was associated with episodes of bleeding and a decrease in follicle stimulating hormone level on two occasions; however details of concomitant medications and relevant medical history were not provided. No further bleeding episodes were experienced following cessation of the face cream. A 42-year old man was found to have chest pain and a tumour like swelling 8 × 6cm in size in his right breast after taking a combination of ginseng, minerals and vitamins (Pharmaton® Complex) containing 240 mg/day of ginseng for 3 months (the recommended dose is 40 to 80 mg/day).[170] Symptoms had resolved 3 weeks after ingestion of the ginseng containing product was discontinued.

3.2 Diuretic Resistance

A 63-year-old man experienced diuretic resistance 10 days after daily ingestion of 10 to 12 tablets of a germanium-containing ginseng preparation (Uncle Hsu's Korean ginseng). Following cessation of the tablets the symptoms improved and after re-challenge they returned. The authors concluded that the problem was more likely to be caused by the germanium than the ginseng.[162]

3.3 Stevens-Johnson Syndrome

A 27-year-old man experienced typical Stevens-Johnson syndrome (bilateral conjunctivitis, dry cough, a macular rash on his face, painful erosions on his mouth and urogenital mucosa, corneal

Table VIII. Adverse events reported in uncontrolled trials of ginseng combination preparations

Trial	n	Patient population	Preparation and dose	Treatment duration	Adverse events reported (no of patients)
Garay Lillo[134]	310	Elderly patients	G115®+ 40mg	6mo	digestive disorders, diarrhoea, euphoria, nervousness, raised blood pressure (13)
Garay Lillo et al.[139]	103	Patients with psycho-emotional deficit disorders	G115®+ 40mg	12mo	26 patients withdrew for reasons unrelated to the medication. No adverse effects or intestinal intolerance noted.
Kuroda et al.[141]	162	Patients with genitourinary cancer	Hochuekkito 7.5g	Average of 20wk	Pain around xiphoid process, nausea/vomiting, chest pain, stomatitis, loss of appetite, liver function problems, skin rash, back pain, anxiety (12)
Horii and Maekawa[142]	53	Patients with lumbago or lower abdominal discomfort	Hochuekkito 7.5g	4wk	Nausea, stomach irritation, pain around xiphoid process, hot flushes (4)
Barsom and Weger[145]	101	Patients with various urinary complaints	Ginseng with vitamin E and royal jelly	4wk	Stomach problems (1)
Xin et al.[146]	186	Patients with premature ejaculation	SS cream 0.1g	Single dose	Mild local irritation (11), delayed ejaculation >30 minutes (4)

G115®+ = standardised ginseng extract, 4% ginsenosides, with vitamins and minerals (Pharmaton SA, Lugano, Switzerland); **Hochuekkito** = *Astralgi radix*, Astractyodis, *Lanceae rhizoma*, *Ginseng radix*, *Angelicae radix*, *Bupleuri radix*, *Zyzyphi fructos*, *Auranti nobilis pericarpium*, *Glycyrrhizae radix*, *Cimicifugae rhizoma* and *Zingiberis rhizoma*; **n** = number of study participants; **SS cream** = *Bufonis venenum*, *Angelicae gigantis radix*, *Cistanchis herba*, *Torilis semen*, *Ginseng radix alba* (white ginseng root), *Zanthoxyli fructos*, *Asiasari radix*, *Caryophylli flos* and *Cinnamomi cortex*.

ulceration and widespread purpuric macules) 3 days after taking two ginseng tablets a day for 3 days.[163] The patient was a regular ginseng user and had not taken any other medication the week before the onset of symptoms. The authors indicate that the ginseng preparation may have been contaminated; the sample was not chemically analysed.

3.4 Psychiatric Conditions

A 35-year-old woman with depressive illness who was maintained on lithium carbonate and amitriptyline experienced a manic episode requiring hospital admission 10 days after interrupting her therapy and starting treatment with one tablet of ginseng a day. Her symptoms improved following cessation of ginseng and a return to her previous medication.[164] It is debatable whether the symptoms were not, at least in part, caused by the cessation of lithium. Five in-patients with diagnoses of schizophrenia were observed to become generally irritable, uncooperative with their treatment programmes and overactive with disturbed sleep after smoking ginseng-containing cigarettes. After stopping smoking these cigarettes their behaviour was seen to improve.[165]

3.5 Cerebral Arteritis

A 28-year-old woman was admitted to hospital with severe headache 6 days after ingesting a bowl of extract (approximately 200ml) made from 60 slices of ginseng root (approximately 25g dry weight) that was stewed with 400ml rice wine (22% alcohol). Eight hours after drinking the extract she developed explosive headache, nausea and vomiting and chest tightness. Cerebral angiograms demonstrated appearances consistent with cerebral arteritis. The headache gradually resolved over the next 10 days. The authors conclude that the close temporal association between ginseng intake and the onset of symptoms suggests a causal relationship.[166]

3.6 Agranulocytosis

Four non-Chinese patients developed life-threatening agranulocytosis while taking Chinese herbal medicines for relief of arthritis and back pain (Long Life Brand Ginseng Hui Sheng Tsaitsaowan and Sanlungpai Ginseng Hui Sheng Tsaitsaowan; Nan Lien Pharmaceutical Company Ltd, Hong Kong and Taiwan). Subsequent analysis of the herbal preparations revealed the presence of undeclared aminopyrine and phenylbutazone, both of which are known to cause agranulocytosis. The authors conclude that these contaminants were responsible for the observed symptoms in these patients.[167]

3.7 Eye Symptoms

Two cases of 'ginseng poisoning' associated with mydriasis and disturbance in accommodation with dizziness and semi-consciousness have been reported.[168]

3.8 Hypertension

A young man presented to his doctor with hypertension, shortness of breath, dizziness and inability to concentrate. He had been taking ginseng supplements for three years. Following cessation of the ginseng supplements his symptoms improved and did not recur.[169] A female patient with hypertension, who was receiving no other medication, reported an increase in her blood pressure from between 160/90 and 240/100 to 280/120mm Hg following treatment with ginseng (Ginzin tablets, Ferrosan) for a few days.[171] Three to 4 days after cessation of the ginseng product her blood pressure had fallen to 240/100mm Hg and treatment with a β-blocker was commenced.

3.9 Pneumonitis

Eighty-seven cases of pneumonitis have been reported in patients with chronic liver disease following treatment with Sho-saiko-to (which contains *P. ginseng*) alone or in combination with interferon.[172-176] The majority of patients recovered following cessation of therapy or high dose oral prednisolone; nine patients died.

3.10 Herb-Drug Interactions

Four reports of possible herb-drug interactions were identified; two reports of a possible interaction with phenelzine,[177-179] one with warfarin[180] and one with alcohol.[181]

3.10.1 Phenelzine

A 64-year-old woman described symptoms of headache and tremulousness when ginseng (Natrol High and ginseng tea) was added to her therapy of phenelzine. Three years later, whilst still taking phenelzine she experienced similar symptoms on ingesting ginseng capsules.[177,178] A 43-year-old woman who had had a long standing depressive illness and whose medication included phenelzine 45 mg/day, triazolam 0.5 mg/day and lorazepam 4 mg/day experienced an improvement of her depression which escalated into manic like symptoms whilst taking a combination of ginseng and bee pollen. When the ginseng preparation was discontinued she no longer benefited from any therapeutic effect from the phenelzine.[179] The clinical significance of these reported interactions is yet to be properly evaluated, especially the latter episode involving a combination of ginseng and bee pollen, which can be of widely varying character.

3.10.2 Warfarin

A 47-year-old man with a St Jude-type mechanical heart valve in the aortic position receiving warfarin to prevent embolic events, started taking three capsules a day of a standard ginseng extract (Ginsana®). His International Normalised Ratio (INR) which had been stable for the previous 9 months declined to 1.5 (target range 2.5 to 3.5), 2 weeks after commencing ginseng supplementation and returned to within the target range on cessation of the ginseng capsules.[180] Using the Naranjo assessment method, the authors rated the interaction as probable;[182] however; a clear resolution of the case report is difficult. A subsequent assessment in a rat model showed no significant impact of gin-

seng on the pharmacodynamics or pharmacokinetics of warfarin.[183]

3.10.3 Alcohol

An open, non-randomised clinical trial of 14 healthy volunteers suggests that *P. ginseng* can enhance the blood alcohol clearance rate. Forty minutes after the administration of alcohol and ginseng the blood alcohol level was 30% lower than following alcohol ingestion alone.[182]

4. Evidence from Epidemiological Studies

Six epidemiological studies were identified.[184-189] Three case control studies of cancer in Korea in over 10 000 patients do not provide any information regarding adverse events.[184,185,189] A further case control study in patients with oligoasthenospermia does not contain details of any untoward effects experienced during the trial.[186] A retrospective cohort study of 1800 elderly patients taking a combination product containing vitamins, minerals and a standardised ginseng extract (G115®), reported the following adverse events: epigastric disorders, hypertension, muscular pain and erythema. The authors reported no clear relationship with the treatment for any of the reported adverse events.[187] An investigation of 133 long-term ginseng users who had been taking ginseng regularly for at least 1 month and were then followed for 2 years described the following symptoms: morning diarrhoea, skin eruptions, demulcent effects on the throat, sleeplessness, nervousness, hypertension, euphoria, oedema, decreased appetite, depression, hypotension and amenorrhoea. High doses (15 g/day) resulted in depersonalisation and confusion in four patients and depression was reported with doses above 15 g/day. The authors also defined a 'ginseng abuse syndrome' characterised as hypertension together with nervousness, sleeplessness, skin eruptions and morning diarrhoea which was reported by 14 of the patients. Participants took a wide variety of commercial ginseng preparations including roots, capsules, tablets, teas, extracts, cigarettes, chewing gum and candies and these contained a variety of types of ginseng including *P. ginseng*, *Panax quinquefolius*, Siberian ginseng and desert ginseng. Dosages and administration methods also varied.[188]

5. Evidence from Spontaneous Reporting Schemes

5.1 The WHO Collaborating Centre for International Drug Monitoring

As of May 2001, reports detailing 378 adverse events had been received from the national drug safety bodies of 18 countries; 168 of these relate to ginseng monopreparations (table IX), 169 to ginseng in combination with vitamins and minerals and 42 to ginseng in combination with other substances including salicylic acid, crataegus extract, royal jelly, caffeine and guarana (table X). The WHO cautions that the information from their database is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction and that the information does not represent the opinion of the WHO. Additional information was available for 178 of these reactions from 86 individual patients. Forty-three of these reports relate to ginseng alone and 43 to ginseng in combination with other substances.

5.1.1 Ginseng Monopreparations

Ginseng was the only suspected drug in 25 cases although one patient was taking other medication concomitantly. The adverse event was described as a drug interaction in two cases; between ginseng, vitamin B complex and sertraline resulting in a reduction of therapeutic response and between ginseng and warfarin resulting in a decreased INR. In 11 cases a definite improvement was seen following cessation of ginseng; two patients showed no improvement and in 30 cases this information is not provided. Rechallenge was performed in two cases; in both instances this resulted in a recurrence of symptoms (diarrhoea and aphasia, dizziness, syncope and tremor). No information regarding causality was provided in 24 cases; however, the relationship was believed to be possible in 14

cases, probable in four cases (diarrhoea, agitation and nervousness, nausea and vomiting, abdominal pain and nausea) and certain in two cases (nausea and vertigo and dizziness, dyspnoea and palpitation). Twenty-one patients recovered without sequelae, two had not yet recovered at the time of reporting and in the remaining 20 patients the outcome was unknown.

5.1.2 Ginseng Multipreparations

Of the 43 patients, the ginseng containing product was the only suspected drug in 33 cases although six of these were taking other medications concomitantly. In 15 cases a definite improvement was seen following dechallenge whilst five patients showed no improvement. Rechallenge was performed in seven cases, all of which showed a

Table IX. Reports of adverse events associated with ginseng monopreparations from the WHO Collaborating Centre for International Drug Monitoring Database

Type of adverse event (number of reports)
Body as a whole – general disorders (21) [fever (3), allergy (2), fatigue (1), asthenia (1), mouth oedema (1), peripheral oedema (1), syncope (1), rigors (1), halitosis (1), pain (1), temperature changed sensation (1), death (1), hot flushes (1), chest pain (2), decreased therapeutic response (1), medicine ineffective (1), unexpected therapeutic effect (1)]
Cardiovascular disorders (7) [hypertension (6), heart murmur (1)]
Central and peripheral nervous system disorders (18) [headache (4), dizziness (4), hypertonia (2), aphasia (1), coma (1), neuropathy (1), paraesthesia (1), leg cramps (1), extrapyramidal disorder (1), tremor (1), vertigo (1)]
Gastrointestinal disorders (20) [nausea (8), diarrhoea (4), abdominal pain (3), vomiting (2), haematemesis (1), flatulence (1), glossitis (1)]
Heart rate and rhythm disorders (5) [arrhythmia (2), palpitation (2), tachycardia (1)]
Liver and biliary system disorders (10) [γ-glutamyl transferase increased (3), hepatic enzymes increased (2), abnormal hepatic function (2), bilirubinaemia (1), hepatitis (1), ALT increased (1)]
Metabolic and nutritional disorders (5) [aggravated diabetes mellitus (2), creatinine phosphokinase increased (1), alkaline phosphatase increased (1), hypocalcaemia (1)]
Musculoskeletal system disorders (3) [musculoskeletal pain (1), rhabdomyolysis (1), myalgia (1)]
Other special senses disorders (1) [taste loss (1)]
Platelet, bleeding and clotting disorders (6) [prothrombin decreased (2), prothrombin increased (1), haemorrhage NOS (1), thrombocytopenia (1) purpura (1)]
Psychiatric disorders (23) [insomnia (5), nervousness (3), manic reaction (3), amnesia (3), somnolence (2), anorexia (1), anxiety (1), emotional lability (1), hallucination (1), sleep disorder (1), depression (1), abnormal thinking (1)]
Respiratory system disorders (5) [dyspnoea (3), sinusitis (1), rhinitis (1)]
Skin and appendage disorders (35) [rash (12), urticaria (6), pruritis (4), angioedema (3), alopecia (2), Stevens-Johnson syndrome (2), increased sweating (1), epidermal necrolysis (1),hypertrichosis (1), abnormal pigmentation (1), dermatitis (1), erythema multiforme (1)]
Urinary system disorders (3) [nocturia (1), pyuria (1), abnormal renal function (1)]
Vascular (extracardiac) disorders (1) [flushing (1)]
Vision disorders (1) [chromatopsia (1)]
White cell disorders (4) [agranulocytosis (2), eosinophilia (1), leucopenia (1)]

NOS = not otherwise specified.

recurrence of symptoms (bloody diarrhoea, anaphylactoid reaction, circulatory failure, diarrhoea and vomiting, melena, nausea, atrial fibrillation, and arrhythmia). The relationship between the adverse event and the drug was believed to be unlikely in two cases, possible in 14 cases and probable in four cases (bloody diarrhoea, agitation and nervousness, erythema multiforme and delirium and tremor). Following the adverse event, 18 patients recovered without sequelae, four had not yet recovered at the time of the report, one had died, unrelated to the drug and one had recovered with

Table X. Reports of adverse events associated with ginseng combination products from the WHO Collaborating Centre for International Drug Monitoring database

Type of adverse event (number of reports)
Body as a whole - general disorders (13) [asthenia (2), fever (2), anaphylactoid reaction (1), allergy (1), hot flushes (1), peripheral oedema (1), back pain (1), rigors (1), chest pain (1), unexpected therapeutic effect (1), fatigue (1)]
Cardiovascular disorders - general (4) [circulatory failure (1), dependent oedema (1), portal hypertension (1), hypertension (1)]
Central and peripheral nervous system disorders (16) [headache (3), paraesthesia (3), hyperkinesia (2), dizziness (2), dyskinesia (1), tremor (1), coma (1), involuntary muscle contractions (1), speech disorder (1), convulsions (1)]
Endocrine disorders (1) [thyroid disorder (1)]
Foetal disorders (2) [congenital abnormality NOS (1) skin malformation (1)]
Gastrointestinal system disorders (62) [vomiting (20), nausea (10), dyspepsia (8), abdominal pain (7), diarrhoea (4), bloody diarrhoea (2), constipation (2), gastritis (2), melaena (2), gastrointestinal haemorrhage (1), oesophageal stricture (1), stomatitis (1), gingivitis (1), dysphagia (1)]
Heart rate and rhythm disorders (14) [tachycardia (7), arrythmia (3), atrial fibrillation (1), torsade de pointes (1), extrasystoles (1), palpitation (1)]
Liver and biliary system disorders (14) [hepatitis cholestatic (3), jaundice (3), hepatic enzymes increased (2), hepatocellular damage (2), hepatitis (1), bilirubinaemia (1), AST increased (1), ALT increased (1)]
Metabolic and nutritional disorders (2) [weight decrease (1), hyperlipaemia (1)]
Musculoskeletal system disorders (1) [myositis (1)]
Myo/endo/pericardial and valve disorders (2) [myocardial infarction (1), angina pectoris (1)]
Platelet, bleeding and clotting disorders (9) [purpura (4), coagulation time increased (2), thrombocytopenia (2), clotting disorder (1)]
Psychiatric disorders (27) [somnolence (5), nervousness (4), agitation (3), delusion (2), hallucination (2), insomnia (2), manic reaction (2), aggressive reaction (1), anorexia (1), depersonalisation (1), psychosis manic depressive (1), sleep disorder (1), anxiety (1), delirium (1)]
Reproductive disorders, female (2) [unintended pregnancy (1), intermenstrual bleeding (1)]
Skin and appendage disorders (36) [rash (10), urticaria (8), pruritus (6), angioedema (4), erythema multiforme (3), alopecia (1), contact dermatitis (1), dermatitis (1), allergic vasculitis (1), bullous eruption (1)]
Vascular (extracardiac) disorders (1) [vascular disorder (1)]
Vision disorders (4) [conjunctivitis (2), eye pain (1), abnormal vision (1)]

NOS = not otherwise specified.

sequelae although no further information was provided.

5.2 US Food and Drug Administration

The most recent update available (October 1998) of the web report of the Special Nutritionals Adverse Event Monitoring System included 117 reports associated with products containing ginseng or *P. ginseng*, including 11 deaths. This is a voluntary scheme in which sources of information include the FDA's Medwatch programme, FDA's field offices, other Federal, State and local public health agencies and letters and phone calls from consumers and healthcare professionals. In all but 19 cases, the products involved were combination preparations of which ginseng or *P. ginseng* was listed as one of a large number of ingredients, including ma-huang, liquorice, ginger, astragalus and cola nut. Ten patients reported 19 adverse events in which ginseng was the only suspected drug (table XI), the remaining nine reports include ginseng as one of up to nine other suspected herbal medications. No information regarding outcomes or causality was available.

Table XI. Adverse events reported to the US Food and Drug Administration Office of Special Nutritionals in which ginseng monopreparations were the only suspected drug

Type of adverse event (no. of reports)
Body as a whole – general disorders (3)
[chest pain (1), pale (1), allergic reaction (1)]
Central and peripheral nervous system disorders (3)
[dizziness (1), headache (1), speech disorder (1)]
Gastrointestinal system disorders (9)
[vomiting (3), nausea (3), diarrhoea (1), scratched oesophagus (1), stomach pains (found piece of glass in bottle) (1)]
Heart rate and rhythm disorders (1)
[heart pounding (1)]
Psychiatric disorders (1)
[anxious (1)]
Reproductive disorders, female (1)
[abnormal uterine bleeding (1)]
Vision disorders (1)
[blurred vision (1)]

5.3 UK Medicines Control Agency

Between July 1963 and May 2001, the UK MCA had received reports of adverse events with *P. ginseng* for 17 patients with no fatal outcomes. These patients had reported 36 adverse reactions, 31 after ingestion of ginseng alone (table XII) and five following a combination product containing *P. ginseng*, vitamins and minerals (dizziness, fatigue, feeling abnormal, headache and tunnel vision). Two drug interactions were reported with a ginseng monopreparation; however, no further details were provided and no information regarding outcomes or causality for any of the adverse events was available.

5.4 German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

A total of 15 case reports for *P. ginseng* had been received by the BfArM prior to May 2001, 13 of these for ginseng combination products and two for ginseng monopreparations (abdominal pain and increase in prothrombin). In 12 cases the ginseng product was the only suspected drug. Amongst the adverse reactions reported for ginseng combination products there were seven gastrointestinal problems, four liver related disorders, two cardiovascular disorders, myalgia, herpes zoster, face oedema, circulatory failure, anaphylactoid reaction, eye pain, hallucination, dyskinesia and hyperkinesia. No further information was provided.

6. Data from Ginseng Manufacturers

Information was received from two of the 12 manufacturers/distributors of ginseng products contacted.

As of July 2000, Pharmaton (Boehringer Ingelheim) had received an unspecified number of reports regarding adverse events experienced by patients for Ginsana®, a standardised ginseng extract, that included problems of a psychiatric and gastrointestinal nature, disorders of the central and peripheral nervous system, reproductive system, respiratory system, cardiovascular system, urinary

Table XII. Reports of adverse events for ginseng monopreparations from the UK Medicines Control Agency

Type of adverse event (number of reports)
Cardiovascular disorders (2) [drop in blood pressure (1), arrhythmia (1)]
Gastrointestinal system disorders (4) [dyspepsia (1), nausea (1), gastric ulcer (1), ulcerative oesophagitis (1)]
General disorders (6) [dizziness (1), fatigue (2), feeling hot (1), pyrexia (1), sedation (1), drug interaction NOS (2)]
Haemopoetic disorders (2) [iron deficiency anaemia (1), eosinophilia (1)]
Hepatobiliary disorders (1) [γ-glutamyl transferase increased (1)]
Metabolic and nutritional disorders (1) [aggravation of diabetes mellitus (1)]
Musculoskeletal disorders (1) [musculoskeletal pain (1)]
Neurological disorders (3) [headache NOS (1), motor neurone disease (1), paraesthesia (1)]
Psychiatric disorders (3) [mania (1), confusion (1), hallucinations (1)]
Renal and urinary disorders (1) [renal failure (1)]
Reproductive disorders (2) [gynaecomastia (1), nipple disorder (1)]
Skin and subcutaneous tissue disorders (3) [rash (3)]

NOS = not otherwise specified.

system, and musculoskeletal system. There were also several heart rate and rhythm disorders, platelet, bleeding and clotting disorders, skin reactions and disorders of the body as a whole.[190] Insufficient information was available to comment on causality.

Between July 1994 and July 1999, Pharmaton had also received an unspecified number of case reports of adverse events for the combination product Pharmaton® Complex that contains a standardised ginseng extract, minerals and vitamins. Of these several were considered serious (melena, abnormal hepatic function and acute renal failure, tinnitus, abdominal pain, cerebral thrombosis, allergic reaction and anaphylactoid reaction). None of the adverse events was fatal and after careful consideration of the circumstances surrounding each event Pharmaton® Complex was not believed to be a causal factor in any case.[190]

As of September 2001, Arkopharma Laboratoires Pharmaceutiques, Carros, France, had received one medically unconfirmed report of a dermatological reaction (skin eruption) which occurred during treatment with ginseng root powder (Ginseng Arkocaps®) [1200 mg/day; 390 mg/capsule, 8% ginsenosides]. The patient was also receiving treatment with fenofibrate, glibenclamide (glyburide) and naftidrofuryl. A later rechallenge with naftidrofuryl was without adverse event. Causality was rated as 'plausible' for ginseng, glibenclamide and fenofibrate.

7. Discussion

As with pharmaceutical products, the establishment of a causal relationship between the ingestion/application of a herbal product and a subsequent adverse event is difficult. There are additional difficulties with herbal products due to the potential for contamination, adulteration and mislabelling. The bulk of the data presented should be evaluated with a degree of caution.

Information from clinical trials is especially difficult to interpret since trials designed to assess efficacy rarely collect rigourous information on adverse events. This was evidenced by 50% of trials not providing such information in the report. Procedures for collecting information on adverse events may differ between trials and countries and may also differ between different centres in a multicentre trial. Often patients are exposed for short periods and each trial includes a relatively small number of patients so reducing the possibility of rare and delayed adverse events being observed. With these caveats in mind this review identified 146 clinical trials which represented the exposure of over 8500 individuals to ginseng preparations (over 3500 to monopreparations) with relatively few adverse events being reported. The most frequent of these were gastrointestinal or sleep related in nature with few precipitating withdrawal of the patient from the study and no appar-

ent differences between the ginseng and control groups.

The data obtained from spontaneous reporting schemes is often insufficient thus not allowing conclusive attribution of causality. Patients often take multiple medications and this information may not be readily available. There is also evidence that patients do not report all adverse events experienced after taking over the counter medications whether herbal or conventional[191] and that hospital doctors under-report adverse events.[192] It is possible that there is some overlap between the data from the various reporting schemes and between the data provided by ginseng manufacturers. Collation of the available data for mono-preparations suggests that adverse events are on the whole mild and reversible although serious events have occurred. Interpretation of the data regarding ginseng in combination with other ingredients is more difficult as many of the constituents within combination products have recognised adverse effects themselves.

Case reports provide more detailed information about individual patients; however, identification of *P. ginseng* as a contributor is virtually impossible in most cases. In 22 of the 27 reports no detail was provided given regarding the type of ginseng or the dose involved, and little information is provided regarding temporal relationships and other possible contributing factors. There have also been instances where the ginseng product has been analysed and shown to be contaminated or mislabelled.[162,167,193] More extensive reporting of adverse events associated with herbal products is necessary to improve safety evaluation. Ideally, reports should include the trade name and constituents of the product, a chemical profile, the dose and duration of treatment and an assessment of causality.

Many of the more generally accepted adverse events associated with the use of *P. ginseng* relate to a prospective study carried out in the 1970s in which 133 regular users of ginseng were observed for 2 years.[188] From the adverse effects observed the author was able to define a 'ginseng abuse syndrome' which occurred in 14 of the patients. However, patients used a wide variety of different ginseng doses, administration methods and preparations, some of which contained other stimulants and may explain some of the symptoms observed. The same author carried out a further study of two groups of long term users of commercial *P. ginseng* in which group A (n = 10) consisted of users who also used other psychomotor stimulants whilst group B (n = 8) used ginseng only.[72] Fewer adverse effects were seen in the ginseng only group and none of the patients developed 'ginseng abuse syndrome' although the size of the study is small and thus interpretation difficult. It is interesting that 22 of the patients in the original study developed hypertension and yet more recently *P. ginseng* has been shown to lower elevated blood pressure in several studies.[18,83,88]

8. Conclusions

In conclusion, the available data suggest that *P. ginseng* is well tolerated by most users, with the most frequently experienced adverse effects being mild and reversible. Ginseng combination products are associated with more adverse events, presumably due to the other ingredients contained within them. Potential drug interactions have been described with phenelzine, warfarin and alcohol. As *P. ginseng* is highly prized and used extensively in a wide range of products, accurate reporting of adverse events in case reports and clinical trials, and potential contamination and mislabelling of ginseng products are all important factors in the future assessment of possible risk.

Acknowledgements

Joanna Thompson Coon was supported by a research fellowship provided by Pharmaton SA, Lugano, Switzerland.

The authors wish to thank Jongbej Park KMD, Barbara Wider and Katja Schmidt, Department of Complementary Medicine, University of Exeter for the translation of studies from Chinese, Korean, Japanese, Danish, Swedish, French, Spanish, Italian, German and Russian and Esther Prati, Pharmaton SA, Lugano, Switzerland for assistance with locating relevant articles.

References

1. The description of a Tartarian plant called ginseng with an account of its virtues. Philosophical Transactions of the Society of London 1713; XXVIII: 237-247
2. Blumenthal M. Herb sales down 15 percent in mainstream market. HerbalGram 2001; 51: 69
3. Society of Japanese Pharmacopoeia, Tokyo, Japan. Ginseng. Ginseng radix. The Pharmacopoeia of Japan 1991: 642
4. Tu G, Chen C, Fang Q, et al., editors. Radix ginseng (Renshen). Pharmacopoeia of the People's Republic of China 1988: 116-7
5. Ginseng root. Ginseng radix. Ginsengwurzel. Deutsches Arzneibuch. 1991: 10
6. Ginseng. Panax ginseng. Commission nationale de Pharmacopée. Paris, 1989
7. Radix ginseng. Ginsengwurzel. In: Oestereichisches Arzneibuch (Pharmacopoea Austriaca). Wien; Verlag der Osterreichischen Staatsdruckemei 1981: 923-5
8. Reynolds JEJ, editor. Ginseng. Martindale the extra pharmacopoeia. London: The Royal Pharmaceutical Society, 1996: 1710
9. O'Hara M, Kiefer D, Farrell K, et al. A review of 12 commonly used medicinal herbs. Arch Fam Med 1998; 7: 523-36
10. Vogler BK, Pittler MH, Ernst E. The eficacy of ginseng: a systematic review of randomised clinical trials. Eur J Clin Pharmacol 1999; 55: 567-75
11. Rote Liste® Service GmbH, Frankfurt. Rote Liste 1999. Aulendorf, Germany: Editio Cantor Verlag, 1999
12. Wiklund IK, Mattsson L-A, Lindgren R, et al. Effects of a standardised ginseng extract on quality life and physiological parameters in symptomatic postmenopausal women: a double blind, placebo controlled trial. Int J Clin Pharmacol Res 1999; XIX: 89-99
13. Engels H-J, Wirth JC. No erogenic effects of ginseng (Panax ginseng C.A.Meyer) during graded maximal aerobic exercise. J Am Diet Assoc 1997; 97: 1110-5
14. Gianoli AC, Riebenfeld D. A double blind study to assess the tolerability and efficacy of the standardised ginseng extract G115 with special regard to its effect on the resistance of the organism to external influences. Cytobiol Rev 1984; 8: 177-86
15. Scaglione F, Catteneo G, Alessandria M, et al. Efficacy and safety of the standardised ginseng extract G115 for potentiating vaccination against common cold and/or influenza syndrome. Drugs Exp Clin Res 1996; 22: 65-72
16. Allen JD, McLung J, Nelson AG, et al. Ginseng supplementation does not enhance healthy young adults' peak aerobic exercise performance. J Am Coll Nutr 1998; 17: 462-6
17. Mulz D, Scardigli G, Jans G, et al. Long term treatment of the psycho-asthenia in the second half of the life. Pharmazeutische Rundschau 1990; 12: 86
18. Han KH, Choe SC, Kim HS, et al. Effect of red ginseng on blood pressure in patients with essential hypertension and white coat hypertension. Am J Chin Med 1998; XXVI: 199-209
19. Cartwright L. You and ginseng: recent human trials. Aust J Pharm 1982, 62: 47
20. Fulder S, Kataria M, Gethyn-Smith B. A double blind clinical trial of *Panax ginseng* in aged subjects. Proceedings of the 4th International Ginseng Symposium; 1984 Sep 18-20; Daejeon, Korea, 223
21. Kim NH, Lee HM, Choi CH, et al. Clinical effect of Korean red ginseng on osteoporosis. J Ginseng Res 1998; 22: 114-21
22. Kim YC, Hong YK, Shin JS, et al. Effect of Korean red ginseng on sexual dysfunction and serum lipid level in old aged men. Korean J Ginseng Sci 1996; 20: 125-32
23. Kim S-H, Lee S-R, Do J-H, et al. Effects of Korean red ginseng and western ginseng on body temperature, pulse rate, clinical symptoms and the hematological changes in human. Korean J Ginseng Sci 1995; 19: 1-16
24. Medvedev MA. The effect of ginseng on the working performance of radio operators. Papers on the study of ginseng and other medicinal plants of the Far East. Vladivostok, 1963: 237-9
25. Forgo I. The duration of effect of the standardised Ginseng Extract G115 in healthy competitive athletes. Notabene Medici 1985; 15: 636-40
26. Engels H-J, Said JM, Wirth JC. Failure of chronic ginseng supplementation to affect work performance and energy metabolism in healthy adult females. Nutr Res 1996; 16: 1295-305
27. Smith K, Engels H-J, Martin J, et al. Efficacy of a standardised ginseng extract to alter psychological function characteristics at rest and during exercise stress [abstract]. Med Sci Sport Exerc 1995; 27: S147
28. D'Angelo L, Grimaldi R, Caravaggi M, et al. A double blind, placebo controlled clinical study on the effect of a standardised ginseng extract on psychomotor performance in healthy volunteers. J Ethnopharmacol 1986; 16: 15-22
29. Scaglione F, Ferrara F, Dugnani S, et al. Immunomodulatory effects of two extracts of *Panax ginseng* C.A. Meyer. Drugs Exp Clin Res 1990; 16: 537-42
30. Quiroga DHA, Imbriano AE. The effect of *Panax ginseng* extract on cerebrovascular deficits. Orientacion Medica 1979; 28: 86-7
31. Dorling E. Do ginsenosides influence the performance? Notabene Medici 1980; 10: 241-6
32. Forgo I, Kayasseh L, Staub JJ. Effect of a standardised ginseng extract on general well-being, reaction capacity, pulmonary function and gonadal hormones. Med Welt 1981; 32: 751-6
33. Van Schepdael P. Les effets du ginseng G115 sur la capacite physique de sportifs d'endurance [in French]. Acta Ther 1993; 19: 337-47
34. Forgo I. Effect of drugs on physical performance and hormone system of sportsmen [in German]. Munch Med Wochenschr 1983; 124: 822-4
35. Collomp K, Wright F, Collomp R, et al. Ginseng et exercise supramaximal. Sci Sports 1996; 11: 250-1
36. Scaglione F, Cogo R, Cocuzza C, et al. Immunomodulatory effects of *Panax ginseng* C.A. Meyer (G115) on alveolar macrophages from patients suffering with chronic bronchitis. Int J Immunother 1994; 10: 21-4
37. Quiroga HA. Comparative double blind study of the effect of Ginsana and hydergin on cerebrovascular deficits. Orientacion Medica 1982; 31: 201-2
38. Kennedy D, Scholey A, Wesnes KA. Dose-dependent enhancement of cognitive performance in young volunteers by a single dose of ginseng. Int J Neuropsychopharmacol 2000; 3 Suppl. 1: S365
39. Sorensen H, Sonne J. A double masked study of the effets of ginseng on cognitive functions. Curr Ther Res 1996; 57: 959-68
40. Srisurapanon S, Rungroeng K, Apibal S, et al. The effect of standardised ginseng extract on peripheral blood leukocytes and lymphocyte subsets: a preliminary study in young healthy adults. J Med Assoc Thai 1997; 80: S81-5

41. Cherdrungsi P, Rungroeng K. Effects of standardised ginseng extract and exercise training on aerobic and anaerobic exercise capacities in humans. Korean J Ginseng Sci 1995; 19: 93-100
42. Siegl C, Siegl HJ. Die mogliche revision von einbussen an psychiscen fahigkeiten im hoheren alter [in German]. Therapiewoche 1979; 29: 4206-16
43. Gundling K, Brodsky Z, Robbins J, et al. Panax ginseng enhances IGM and IGA antibody titers after influenza vaccination [abstract]. Altern Ther Health Med 2001; 7: 104
44. Chang YS, Park CI. The effect of *Panax ginseng* on the postoperative radiation complication in cervical cancer patients. Seoul J Med 1980; 21: 187-93
45. Kuwashima K, Kaneko H, Nakanishi K. Studies of clinical effects of ginseng: 1st report; a double blind study of unsettled complaint improving effect of ginseng. Proceedings of the 3rd International Ginseng Symposium; 1980 Sep 8-10; Seoul, Korea, 191
46. Kuwashima K, Kaneko H, Nakanishi K. Studies on clinical effects of ginseng: 2nd report; Effects of ginseng at acute massive dosage on circulatory function: a study by digital plethysmography. Proceedings of the 3rd International Ginseng Symposium; 1980 Sep 8-10; Seoul, Korea, 196
47. Koo KH, Joo CN. Clinical study on the efficacy of Panax ginseng C.A.Meyer on acute viral (B) hepatitis – (II). Korean J Ginseng Sci 1983; 7: 125-32
48. Wyss V, Ganzit GP, Rienzi A, et al. Effetti della radice di ginseng sul lavoro muscolare sottomassimale e massimale dell'uomo [in Italian]. Medicina dello Sport 1987; 40: 7-16
49. Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. Int J Impot Res 1995; 7: 181-6
50. Choi KM, Lee EJ, Kim YH, et al. Effects of red ginseng on the lipid peroxidation of erthrocyte and antioxidant superoxide dismutase (SOD) activity in NIDDM patients. Korean J Ginseng Sci 1997; 21: 153-9
51. Lee BM, Lee SK, Kim HS. Inhibition of oxidative DNA damage, 8-OHdG, and carbonyl contents in smokers treated with antioxidants (vitamin E, vitamin C, beta-carotene and red ginseng). Cancer Lett 1998; 132: 219-27
52. McNaughton L, Egan G, Caelli G. A comparison of Chinese and Russian Ginseng as erogenic aids to improve various facets of physical fitness. Int Clin Nutr Rev 1989; 9: 32-5
53. Hallstrom C, Fulder S, Carruthers M. Effects of ginseng on the performance of nurses on night duty. Comp Med East West 1982; 4: 277-82
54. Teves MA, Wright JE, Welch MJ, et al. Effects of ginseng on repeated bouts of exhaustive exercise [abstract]. Med Sci Sport Exerc 1983; 15: 162
55. Knapik JJ, Wright JE, Welch MJ, et al. The influence of panax ginseng on indices of substrate utilisation during repeated exhaustive exercise in man [abstract]. Fed Proc 1983; 42: 336
56. Johnson A, Jiang N-S, Staba EJ. Whole ginseng effects on human response to demands for performance. Proceedings of the 3rd International Ginseng Symposium; 1980 Sep 8-10; Seoul, Korea, 244
57. Zhao XZ. Anti-senility effect of ginseng-rhizome saponin. J Modern Developments Traditional Med 1990; 10: 579-589
58. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin dependent diabetic patients. Diabetes Care 1995; 18: 1373-5
59. Ziemba AE, Chmura J, Kaciuba-Uscilko H, et al. Ginseng treatment improves psychomotor performance at rest and during graded exercise in young athletes. Int J Sport Nutr 1999; 9: 371-7
60. Scaglione F, Weiser K, Alessandria M. Effects of the standardised ginseng extract G115 in patients with chronic bronchitis. Clin Drug Invest 2001; 21: 41-5
61. Forgo I, Kirchdorfer AM. The effect of different ginsenoside concentrations on physical work capacity. Notabene Medici 1982; 12: 721-7
62. Lee HY, Kim CS. Clinical investigation of Insam (Korean ginseng) on sexual potency. Korean J Urol 1986; 27: 235-40
63. Mulz D, Degenring F. Doping control after a 14 day treatment [abstract]. Pharmazeutische Rundschau 1989; 11: 22
64. Pujol P, Verdaguer-Codina J, Drobnic F, et al. Effects of a ginseng extract alone and combined with other elements on free radical production and hemoglobin reoxygenation following a maximal stress test. Proceedings of the International Pre-Olympic Science Congress: 1996 Jul 10-14; Dallas (TX)
65. Garcia RR. Estudio comparativo de dos farmacos que actuan sobre el envejecimiento cerebral. Prensa Med Argent 1988; 75: 134-9
66. Wang WK, Chen HL, Hsu TL, et al. Alteration of pulse in human subjects by three chinese herbs. Am J Chin Med 1994; 22: 197-203
67. Ding D, Shen T, Cui Y, et al. Effects of red ginseng on the congestive heart failure and its mechanism. Chin J Integrated Traditional West Med 1995; 15: 325-7
68. Shin YO, Cho YK, Ki MK, et al. Effect of Korean red ginseng on immunological markers of persons with human immunodeficiency virus. Proceedings of the 6th International Ginseng Symposium; 1993 Sep 6-9; Seoul, Korea, 56
69. Yamamoto M, Miki S, Deguchi H, et al. Combined effect of red ginseng with xiao-chai-hu-tang in patients with chronic hepatitis. Proceedings of the 6th International Ginseng Symposium; 1993 Sep 6-9; Seoul, Korea, 60
70. Koo KH, Joo CN. Clinical study on the efficacy of *Panax ginseng* C.A Meyer on acute viral (B) hepatits (I). Korean J Ginseng Sci 1983; 7: 115-24
71. Woo YM, Lee HW, Kim JP. The effect of ginseng on the postoperative nutritional status and immune functions of gastric carcinoma patients. Proceedings of the 6th International Ginseng Symposium; 1993 Sep 6-9; Seoul, Korea, 65
72. Siegel RK. Ginseng use among two groups in the United States. Proceedings of the 3rd International Ginseng Symposium; 1980 Sep 8-10; Seoul, Korea, 236
73. Cho YK, Kim YK, Lee I, et al. The effect of korean red ginseng (KRG), Zidovudine (ZDV) and the combination of KRG and ZDV on HIV-infected individuals. J Korean Soc Microbiol 1996; 31: 353-60
74. Forgo I, Kirchdorfer AM. On the question of influencing the performance of top sportsmen by means of biologically active substances. Aerztliche Praxis 1981; 33: 1784-6
75. von Ardenne M, Klemm W. Measurements of the increase in the difference between the arterial and venous Hb-O2 saturation obtained with daily administration of 200mg standardised ginseng extract for four weeks. Panminerva Med 1987; 29: 143-50
76. Lee HY, Paick JS, Lee SW. Efficacy of ginseng extract on patients with oligospermia. Korean J Urol 1988; 29: 950-60
77. Gross D, Krieger D, Efrat R, et al. Ginseng extrakt G115 for the treatment of chronic respiratory diseases: a pilot study

investigating the effects of ginseng extract G115 on pulmonary functions, general functions and oxygenation. Scweiz Z Ganzheits Med 1995; 1: 29-33
78. Reinold E. Der Einsatz von Ginseng in der Gynakologie. Natur Ganzheits Med 1990; 4: 131-4
79. Forgo I. Doping control of top-ranking athletes after a 14-day treatment with Ginsana. Pharmaton SA, Lugano, Switzerland, 1980 (Data on file)
80. Tode T, Kikuchi Y, Hirata J, et al. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int J Gynaecol Obstet 1999; 67: 169-74
81. Yamamoto M, Uemura T, Nakama S, et al. Serum HDL-cholesterol-increasing and fatty liver improving actions of *Panax Ginseng* in high cholesterol diet fed rats with clinical effect on hyperlipidaemia in man. Am J Chin Med 1983; 11: 96-101
82. Wyss V, Gribaudo C, Ganzit GP. Effetti del ginseng su alcuni aspetti della performance fisica in atleti. Medicina dello Sport 1982; 35: 383-9
83. Sohn E-S, Huh B-Y, Lee D-H, et al. The effect of korean ginseng on blood pressure in essential hypertension by oral administration. J Korean Med Assoc 1980; 23: 227-33
84. Gezzi A, Longhi MG, Mazzoleni R, et al. Dermocosmetic activity of ginsenosides. Note II: instrumental evaluation of cutaneous hydration and elasticity. Fitoterapia 1986; 57: 15-28
85. Curri SB, Gezzi A, Longhi MG, et al. Dermocosmetic activity of ginsenosides. Note III: long term evaluation of the moisturising and tonifying effect on the face skin. Fitoterapia 1986; 57: 217-22
86. Okuda H, Yoshida R. Studies on the effects of ginseng components on diabetes mellitus. Proceedings of the 3rd International Ginseng Symposium; 1980 Sep 8-10; Seoul, Korea, 57
87. Ogita S. Clinical effectiveness of Korean ginseng on climacteric disturbances and its possible mechanism of action. Korean J Ginseng Sci 1990; 14: 162-6
88. Imamura Y, Kuwashima K. The effects of red ginseng on blood pressure and the quality of life in essential hypertensives. Proceedings of the 4th International Ginseng Symposium; 1984 Sep 18-20; Daejeon, Korea, 91
89. Yamamoto M, Kumagai A. Long term ginseng effects on hyperlipidemia in man with further study on its actions on atherogenesis and fatty liver in rats. Proceedings of the 4th International Ginseng Symposium; 1984 Sep 18-20; Daejeon, Korea, 19
90. Kaneko H, Nakanishi K, Murakami A, et al. Effect of red ginseng on hemodynamic changes by physical exercise. Proceedings of the 4th International Ginseng Symposium; 1984 Sep 18-20; Daejeon, Korea, 256
91. Sung J, Han K-H, Zo J-H, et al. Effects of red ginseng upon vascular endothelial function in patients with essential hypertension. Am J Chin Med 2000; 28: 205-16
92. Punnonen R, Lukola A. The effect of ginseng on serum total cholesterol, HDL-cholesterol and triglyceride levels in postmenopausal women. Asia Oceania J Obstet Gynaecol 1984; 10: 399-401
93. Kim HK, Choi WY, Cho WY, et al. Effect of ginseng on renal function in patient with renal injury. Korean J Ginseng Sci 1997; 21: 49-52
94. Zuin M, Battezzati PM, Camisasca M, et al. Effects of a preparation containing a standardised ginseng extract combined with trace elements and multivitamins against hepatotoxin induced chronic liver disease in the elderly. J Int Med Res 1987; 15: 276-81
95. Dorling E, Kirchdorfer AM. Ginseng macht wieder fit. Arztliche Praxis 1989; 41: 1867-9
96. Pieralisi G, Ripari P, Vecchiet L. Effects of a standardised Ginseng extract combined with dimethylaminoethanol bitartrate, vitamins, minerals and trace elements on physical performance during exercise. Clin Ther 1991; 13: 373-82
97. Neri M, Andermarcher E, Pradelli JM, et al. Influence of a double blind pharmacological trial on two domains of well-being in subjects with age associated memory impairment. Arch Gerontol Geriatr 1995; 21: 241-52
98. Ussher JM, Dewberry C, Malson H, et al. The relationship between health related quality of life and dietary supplementation in British middle managers: a double blind placebo controlled study. Psychol Health 1995; 10: 97-111
99. Curutchet Ragusin JE, Perez MR, Dalvarade JU. Clinical trial of a new product for the prevention and treatment of symptoms associated with senility. Lugano: Pharmaton, 1980 (Unpublished report)
100. Thommessen B, Laake K. No identifiable effect of ginseng (Gericomplex) as an adjuvant in the treatment of geriatric patients. Aging 1996; 8: 417-20
101. Sandberg F. Clinical effects of ginseng preparations. Z Praklinische Geriatr 1974; 4: 264-8
102. Colombi R. Clinical report on geriatric Pharmaton. Lugano: Pharmaton, 1970 (Unpublished report)
103. Ussher JM, Swann C. A double blind placebo controlled trial examining the relationship between Health Related Quality of Life and dietary supplements. Br J Health Psychol 2000; 5: 173-87
104. Sandberg F, Dencker L. Experimental and clinical tests on ginseng. Z Phytother 1994; 15: 38-42
105. Tesch PA, Johansson H, Kaiser P. The effect of ginseng, vitamins and minerals on the physical work capacity in middle aged men. Lakartidningen 1987; 84: 4326-8
106. Revers WJ, Simon WCM, Popp F, et al. Psychologische Wirkungen eines Geriatrikums auf alte Menschen [in German]. Geriatrie 1976; 6: 418-30
107. Grosse HB, Degenring F, Mulz D. Gincosan bei epileptogenen Hirnleistungsstorungen. Zum einfluss von Gincosan auf kognitive defizite bei langjahrig hospitalisierten epileptikern: Eine plazebokontrollierte Doppelblindstudie [in German]. Psycho 1992; 18: 495-501
108. Warnecke G. Die Behandlung klimakterisher Beshwerden mit einer Wirkstoffcombination ohne Hormone [in German]. Z Ther 1974; 2: 90-5
109. Schmidt UJ. Die Wirkung einer Kombination aus standardisiertem Ginsengextrakt G115, Dimethylaminoathanol, Vitaminen und Mineralstoffen und einzelner ihrer Komponenten auf das biologische Alter, den Blutdruck und die Herzfrequenz von Patienten mit primar chronischer Polyarthritis [in German]. Geriatr Forsch 1992; 2: 111-22
110. Le Faou M. The effect of geriatric pharmaton versus placebo on physical fatigue and recovery. Sport et Medicine 1985; Special Issue: 34-41
111. Liao J, Chen J, Wu Z, et al. Clinical and experimental studies of coronary heart disease treated with Yi-Qi- Huo-Xue injection. J Tradit Chin Med 1989; 9: 193-8
112. Gribaudo CG, Ganzit GP, Baincotti PP, et al. Effects of a natural erogenic product on aerobic capacities in well-trained cyclists. Med Sport (Turin) 1991; 44: 335-43

113. Kiesewetter H, Jung F, Mrowietz C, et al. Hemorrheological and circulatory effects of Gincosan. Int J Clin Pharmacol Ther Toxicol 1992; 30: 97-102
114. Graubaum H-J, Metzner CM, Schneider B. Biologische Wirkstoffkombination zur physischen konditionierung [in German]. Z Phytother 1995; 1: 11
115. Xin Z-C, Choi Y-D, Lee WH, et al. Penile vibratory threshold changes with various doses of SS-cream in patients with primary premature ejaculation. Yonsei Med J 2000; 41: 29-33
116. Le Gal M, Cathebras P, Struby K. Pharmaton capsules in the treatment of functional fatigue: a double blind study versus placebo evaluated by a new methodology. Phytother Res 1996; 10: 49-53
117. Wiklund IK, Karlberg J, Lund B. A double blind comparison of the effect on quality of life of a combination of vital substances including standardised ginseng G115 and placebo. Curr Ther Res 1994; 55: 32-42
118. Garay Lillo J. Double blind clinical study of Geriatric Pharmaton in the processes of involution. Geriatrika 1984; 1: 29-38
119. Hugonot R, Hugonot L, Israel L. Clinical double-blind study of Geriatric Pharmaton against placebo on 98 patients aged 50 and more, during 60 days. Proceedings of the Symposium Vitality, Creativity and Longetivity; 1981 May 21; Paris
120. Kwiencinski H, Lusakowska A, Mieszkowski J. Improvement in concentration following treatment with ginseng/ginkgo biloba combination in patients with chronic cerebrovascular disorders: a double-blind, placebo controlled study. Eur J Clin Res 1997; 9: 59-67
121. Choi H-K, Xin Z-C, Choi Y-D, et al. Safety and efficacy study with various doses of SS cream in patients with premature ejaculation in a double blind, randomised, placebo controlled clinical study. Int J Impot Res 1999; 11: 261-4
122. Wesnes KA, Faleni R, Hefting N, et al. The cognitive, subjective and physical effects of a Ginkgo biloba/*Panax ginseng* combination in healthy volunteers with neurasthenic complaints. Psychopharmacol Bull 1997; 33: 677-83
123. Della Marchina M, Renzi G. Terapia farmacologica protratta in diabetici nid compensati con lievi disturbi cognitivi studio controllato in doppio cieco. Geriatria 1998; 10: 69-83
124. Choi H-K, Jung GW, Moon KH, et al. Clinical study of SS-cream in patients with lifelong premature ejaculation. Urology 2000; 55: 257-61
125. Marasco CA, Ruiz VR, Villagomez SA, et al. Double blind study of a multi-vitamin complex supplemented with ginseng extract. Drugs Exp Clin Res 1996; 22: 323-9
126. Mor G. Effect of Pharmaton capsules on convalescents: a comparative study. Adv Diet Nutr 1988; 47: 106
127. El Nasr MSS, El-Desoky M, Sallam MS, et al. Placebo controlled study of Ginseng in the management of diabetes mellitus. Al-Azhar Med J 1982; 11: 361-6
128. Poggi E, Sforzini D, Lazzati-Crespi GL. On the clinical use of an antidepressive neurotonic vitamin association in ageing disorders. Riv Neropsichiatria Scienze Affini 1972; 18: 93-107
129. Shida K, Shimazaki J, Urano E. Clinical study on male infertility (2nd report). Jap J Fertil Steril 1970; 15: 113-8
130. Cascone A. Controlled investigation of geriatric pharmaton. Lugano: Pharmaton, 1973 (Unpublished report)
131. Alessandrini A. Clinical investigation of geriatric pharmaton. Lugano: Pharmaton, 1971 (Unpublished report)
132. Choi DS, Kim SJ, Lee EJ, et al. Effects of red ginseng on platelet function and lipid metabolism or overweighted noninsulin dependent. Proceedings of the 6th International Ginseng Symposium 1993 Sep 6-9; Seoul, Korea, 109
133. Yuan J, Guo W, Yang B, et al. 116 cases of coronary angina pectoris treated with powder composed of radix ginseng, radix notoginseng and succinum. J Tradit Chin Med 1997; 17: 14-7
134. Garay Lillo J. Study over six months on the efficacy and tolerance of Geriatric Pharmaton. Geriatrika 1987; 3: 49-56
135. Mor G. The effect of a combination of biologically active substances (Geriatric Pharmaton) on the well being of cachetic cancer patients. Adv Diet Nutr 1985; 44: 120
136. Murano S, Lo Russo LRR. Experience with Geriatric Pharmaton. Prensa Med Argent 1984; 71: 178-83
137. Kerkhof GA, Middelkoop HAM, van der Hoeve R, et al. Sleep recordings in the elderly before and after usage of a geriatric preparation. J Interdisciplinary Cycle Res 1989; 20: 57-63
138. Simon WCM, Kirchdorfer AM, Dahse G. Efficiency control of a geriatric preparation containing ginseng by means of Kraepelin's performance test. Med Monatsschr 1977; 31: 39-41
139. Garay Lillo J, Caballero Garcia JC, Cabeza Mauricio G, et al. Long term multicentre study with Pharmaton Complex in adult patients. Geriatrika 1992; 8: 290-5
140. Ishikawa H, Manabe F, Zhongtao H, et al. The hormonal response to HCG stimulation in patients with male infertility before and after treatment with Hochuekkito. Am J Chin Med 1992; 20: 157-65
141. Kuroda M, Kotake T, Sonoda T, et al. Clinical evaluation of hochuekkito for symptoms of malignant neoplasm patients. Hinyokika Kiyo 1985; 31: 173-7
142. Horii A, Maekawa M. Clinical evaluation of hochue-ekki-to on the patients with renal ptosis. Hinyokika Kiyo 1988; 34: 2243-8
143. Mitsukawa S, Kimura M, Ishikawa H, et al. Treatment of male sterility by Hochuekkito. Jap J Fertil Steril 1984; 29: 458-65
144. Ota H, Fukushima M, Kodama H, et al. Effects of Hotyu-ekki-to on the patietns with oligospermia. Jap J Fertil Steril 1987; 32: 624-9
145. Barsom S, Weger N. Steigerung von Abwehrreaktionen, Belastbarkeit und Potenz durch eine Ginseng-Vitamin E-Gelee-Royale Zubereitung [in German]. Erfahrungsheilkunde 1988; 37: 430-7
146. Xin ZC, Choi Y-D, Choi H-K. Efficacy of a topical agent SS cream in the treatment of premature ejaculation: preliminary clinical studies. Yonsei Med J 1997; 38: 91-5
147. Xin Z-C, Choi Y-D, Seong DH, et al. Sensory evoked potential and effect of SS cream in premature ejaculation. Yonsei Med J 1995; 36: 397-401
148. Feng P, Liu LM, Shen YY. Effect of shen mai injection on sIL-2R NK ad LAK cells in patients with advanced carcinoma. Chin J Modern Dev Tradit Med 1995; 15: 87-9
149. Lin SY, Liu LM, Wu LC. Effect of shenmai injection on immune function in stomach cancer patients after chemotherapy. Chin J Modern Dev Tradit Med 1995; 15: 451-3
150. Wang W, Niu RJ, Sum JP. Effects of sheng mai injection on thoracoabdominal motion. Chin J Modern Dev Tradit Med 1993; 13: 91-3
151. Jiang HW, Qiam ZH, Weng W, et al. Clinical study on treating qi-deficiency blood stasis syndrome of angina pectoris with qi xue granule. Chin J Modern Dev Tradit Med 1992; 12: 663-5
152. Li NQ. Clinical and experimental study on shen qi injection with chemotherapy in the treatment of malignant tumout of

digestive tract. Zhongguo Zhong Xi Yi Jie Za Zhi 1992; 12: 582-92
153. Sheng ZL, Lee NY, Ge SP, et al. Clinical study of baoyuang dahuang decoction in the treatment of chronic renal failure. Chin J Modern Dev Tradit Med 1994; 14: 268-70
154. Lu BJ, Rong YZ, Zhao MH. Effect of sheng mai san on lipid peroxidation in acute myocardial infarction patients. Chin J Modern Dev Tradit Med 1994; 14: 712-4
155. Fang J, Jiang J, Luo DC. Effect of shenmai decoction on left ventricular function in patients with coronary heart disease. A randomised, double blind placebo controlled cross over trial. Chin J Int Med 1987; 26: 403-6
156. Zhao MH, Rong YZ, Lu BJ. Effect of shengmaisan on serum lipid peroxidation in acute viral myocarditis. Chin J Modern Dev Tradit Med 1996; 16: 142-5
157. Palmer BV, Montgomery ACV, Monteiro JCMP. Gin Seng and mastalgia [letter]. BMJ 1978; 1 (6122): 1284
158. Koriech OM. Ginseng and mastalgia. 1978; 1 (6126): 1556
159. Greenspan EM. Ginseng and vaginal bleeding [letter]. JAMA 1983; 249: 2018
160. Palop-Larrea V, Gonzalvez-Perales JL, Catalan-Oliver C, et al. Metrorrhagia and ginseng. Ann Pharmacother 2000; 34: 1347-8
161. Hopkins MP, Androff L, Benninghoff AS. Ginseng face cream and unexplained vaginal bleeding. Am J Obstet Gynecol 1988; 159: 1121-2
162. Becker BN, Greene J, Evanson J, et al. Ginseng-induced diuretic resistance. JAMA 1996; 276: 607
163. Dega H, Laporte J-L, Frances C, et al. Ginseng as a cause for Stevens-Johnson syndrome? Lancet 1996; 347: 1344
164. Gonzalez-Seijo J, Romas Y, Lastra I. Manic episode and ginseng: Report of a possible case. J Clin Psychopharmacol 1995; 15: 447
165. Wilkie A, Cordess C. Ginseng – a root just like a carrot? J R Soc Med 1994; 87: 594-5
166. Ryu S-J, Chien Y-Y. Ginseng associated cerebral arteritis. Neurology 1995; 45: 829-30
167. Ries CA, Sahud MA. Agranulocytosis caused by Chinese Herbal Medicines. JAMA 1975; 231: 352-5
168. Lou BY, Li CF, Li PY, et al. Eye symptoms due to ginseng poisoning. Yen Ko Hsueh Pao (CHINA) 1989; 5: 96-7
169. Hammond TG, Whitworth JA. Adverse reactions to ginseng [abstract]. Med J Aust 1981 May; 1 (9): 492
170. Palop V, Catalan C, Rubio E, et al. Ginecomastia en un varon y ginseng. Med Clin(Barc) 1999; 112: 46
171. Nielsen AS. Hypertension af ginsengtabletter? Ugeskr Laeger 1988; 150: 377
172. Nakagawa A, Yamaguchi T, Takao T, et al. Five cases of drug induced pneumonitis due to Sho-saiko-to interferon-alpha or both. Nihon Kyobu Shikkan Gakkai Zasshi 1995; 33: 1361-6
173. Sato A, Toyoshima M, Kondo A, et al. Pnemonitis induced by the herbal medicine Sho-saiko-to in Japan. Nihon Kyobu Shikkan Gakkai Zasshi 1997; 35: 391-5
174. Hatakeyama S, Tachibana A, Morita M, et al. Five cases of pneumonitis induced by sho-saiko-to. Nihon Kyobu Shikkan Gakkai Zasshi 1997; 35: 505-10
175. Tojima H, Yamazaki T, Tokudome T. Two cases of pneumonia caused by sho-saiko-to. Nihon Kyobu Shikkan Gakkai Zasshi 1996; 34: 904-10
176. Ishizaki T, Sasaki F, Ameshima S, et al. Pneumonitis during interferon and/or herbal drug therapy in patients with chronic active hepatitis. Eur Respir J 1996; 9: 2691-6
177. Shader RI, Greenblatt DJ. Bees, ginseng and MAOIs revisited. J Clin Psychopharmacol 1988; 8: 235
178. Shader RI, Greenblatt DJ. Phenelzine and the dream machine: ramblings and reflections [abstract]. J Clin Psychopharmacol 1985; 5: 65
179. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. J Clin Psychopharmacol 1987; 7: 201-2
180. Janetsky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm 1997; 54: 692-3
181. Lee FC, Ko JH, Park JK, et al. Effects of Panax ginseng on blood alcohol clearance in man. Clin Exp Pharmacol Physiol 1987; 14: 543-6
182. Naranjo CA, Busto U, Sellers M, et al. Method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45
183. Zhu M, Chan KW, Ng LS, et al. Possible influences of ginseng on the pharmacokinetics and pharmacodynamics of warfarin in rats. J Pharm Pharmacol 1999; 51: 175
184. Yun T-K, Choi S-Y. A case control study of ginseng intake and cancer. Int J Epidemiol 1990; 19: 871-6
185. Yun T-K, Choi S-Y. Preventative effect of ginseng intake against various human cancers: a case control study on 1987 pairs. Cancer Epidemiol Biomarkers Prev 1995; 4: 401-8
186. Salvati G, Genovesi G, Marcellini L, et al. Effects of *Panax Ginseng* C.A. Meyer saponins on male fertility. Panminerva Med 1996; 38: 249-54
187. Garay Lillo J. Profile of a combination preparation with standardised G115 ginseng extract: a retrospective cohort study. Scweiz Z Ganzheits Med 1998; 10: 97-101
188. Siegel RK. Ginseng abuse syndrome. Problems with the panacea. JAMA 1979; 241: 1614-5
189. Yun T-K, Choi S-Y. Non-organ specific cancer prevention of ginseng: a prospective study in Korea. Int J Epidemiol 1998; 27: 359-64
190. Pharmaton SA, Lugano, Switzerland, Jul 2000 (Data on file)
191. Barnes J, Mills SY, Abbot NC, et al. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face to face interviews with 515 users of herbal medicines. Br J Clin Pharmacol 1998; 45: 496-500
192. Smith CC, Bennett PM, Pearce HM, et al. Adverse drug reactions to a hospital general medical unit meriting notification to the Committee on Safety of Medicines. Br J Clin Pharmacol 1996; 42: 423-9
193. Koren G, Randor S, Martin S, et al. Maternal ginseng use associated with neonatal androgenisation. JAMA 1990; 264: 2866

Correspondence and offprints: Dr *Joanna Thompson Coon*, Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, 25 Victoria Park Road, Exeter, EX2 4NT, United Kingdom.
E-mail: J.Thompson-Coon@exeter.ac.uk