Review of recent reported clinical effects of ginseng. Dias report

Bidstrup, Tanja Busk; Brøsen, Kim; Jensen, M.; Christensen, Lars Porskjær ; Kristiansen, K.

Published in:
International Journal of Horticultural Science

Publication date:
2006

Document Version
Publisher's PDF, also known as Version of record

DIAS report

Review of recent reported clinical effects of ginseng

Tanja Bidstrup, Kim Brøsen,
Martin Jensen, Lars Porskjær Christensen og Karsten Kristiansen

DIAS report Horticulture no. 32 • January 2006

Ministry of Food, Agriculture and Fisheries
Danish Institute of Agricultural Sciences

DIAS report Horticulture no. 32 • January 2006

Review of recent reported clinical effects of ginseng

This reveiw was carried out as a part of the project "Development of scientific and commercial strategies for ginseng in Denmark" as a part of actitvities in Development Centre Aarslev and funded by Ministry of Science, Technology and Innovation, County of Funen and cofunded by a number of private companies. The review was performed with the guidance of senior scientist and project leader Martin Jensen, Danish Institute of Agricultural Sciences (DIAS), Department of Horticulture, professor and head of Research Unit, Lars Porskjær Christensen, DIAS - Department of Food Science and professor Karsten Kristiansen, head of Department of Biochemistry and Molecular Biology, Southern Danish University.

Tanja Busk Bidstrup og Kim Brøsen
Clinical Pharmacology
University of Southern Denmark

Martin Jensen og Lars Porskjær Christensen
Danish Institute of Agricultural Sciences
Research Centre Aarslev
Kirstinebjergvej 10
DK-5792 Aarslev

Karsten Kristiansen
Dept. Biochemistry and Molecular Biology
University of Southern Denmark

DIAS reports primarily contain research results and trial statements aimed at Danish conditions. Also, the reports describe larger completed research projects or acts as an appendix at meetings and conferences. DIAS reports are published in the series:
Plant production, Animal Husbandry and Horticulture.

Prices:
Up to 50 pages: Price DKK 55.00 each
Up to 75 pages: Price DKK 85.00 each
More than 75 pages: Price DKK 110.00 each

Subscribers obtain 25% discount. Subscription can be taken out by contacting:
Danish Institute of Agricultural Sciences
P.O. Box 50, DK-8830 Tjele
Tlf. +45 8999 1028

All DIAS publications can be ordered on the internet:
www.agrsci.dk

Print: www.digisource.dk

ISSN 1397-9876

Introduction

Through the years several *in vitro* and *in vivo* studies have indicated a protective effect of ginseng against development of disease, as well as a possible, positive effect on several disease states. The market for ginseng is greatly increasing, as it is largely used by both healthy individuals, as a nutritional supplement and by patients, often in combination with a prescribed drug. Ginseng appears to be a very difficult drug to investigate, for several reasons. For example, is it possible that a very long duration of treatment is necessary to gain any long term positive effect? Furthermore does a lot of different species of ginseng exist and it is possible that they each have very different properties. The four main species of ginseng are: American, Chinese, Korean, and Japanese. Three medical species are currently recognised: *Panax ginseng* C.A. Meyer (Korean ginseng), *Panax japonicus* C.A. Meyer (Japanese ginseng) and *Panax quinquefolius* (American ginseng) (Bahrke and Morgan, 2000). The main constituents of ginseng root are the saponins or ginsenosides, which are glycosylated steroids and these, are the possible pharmacological active components of ginseng. At least 13 saponins/ginsenosides have been isolated from *P. ginseng* roots. These are named ginsenoside R_x, where x is a, b1, b2, c, d, e, f, g1, g2, g3, h1, h2 or o according to their position on thin layer chromatograms (Shibata et al., 1965). Only two ginsenosides are common to Japanese, Chinese, Korean and American ginseng, namely R_{g2} and R_o (Bahrke and Morgan, 2000). The content of each of the ginsenosides in a ginseng preparation varies a lot and probably depends on several factors such as the species of ginseng, cultivation methods, age of the plant at harvest (generally 6-7 years), season the plant is harvested (autumn is recommended (Bahrke and Morgan, 2000)) and preparation of the root (for example is "red ginseng" the steamed and air-dried root, whereas "white ginseng" is the air-dried root. Ginseng steamed at 120 ^oC has been reported to be more pharmacological active and have a higher content of ginsenosides R_{g3} and R_{g5} than raw ginseng (Kim et al., 2000)). All these different factors may complicate comparison of trials, investigating the efficacy of ginseng used for different indications.

Recent studies indicate that it may not only be the root of ginseng that posses pharmacological activities. Lately have both the leaves and the berries of American ginseng and the berries of Korean *Panax ginseng* shown anti-hyperglycemic activities in diabetic *ob/ob* mice (Dey et al., 2003; Xie et al., 2002; Xie et al., 2004b; Xie et al., 2004a) and the berries of American ginseng have actually shown a more potent anti-hyperglycemic activity than the root (Dey et al., 2003). And to complicate the use of ginseng further, have an investigation shown that some commercial ginseng products actually do not contain any true ginsenosides (Cui et al., 1994). Differences in efficacy and content of ginsenosides of American ginseng (cultivated *Panax quinquefolius L.*) depending on the batch have also been demonstrated (Sievenpiper et al., 2003a).

G115, marketed under the name Ginsana (GLP Ginsana Products SA, Lugano, Switzerland), is an extract of Korean *Panax ginseng* that contains a standardized concentration of 13 ginsenosides and lately this has been used in clinical trial set-ups of the effects of ginseng, to overcome some of the above mentioned problems.

In 1999 Vogler et al. reported the results of a systematic review of double-blind, randomized, placebo-controlled clinical trials of ginseng root extract for any indication (Vogler et al., 1999). Sixteen trials were included and actually 10 of these showed a significant ($P<0.05$), beneficial effect on the measured effect parameters of the respective trials. These effect parameters included physical performance, immunological parameters, psychomotor performance, cognitive behavior and reduction in blood glucose levels in type II diabetic patients. Four of the 16 trials included in the review did not show a significant beneficial effect of ginseng on physical performance, one did not show an effect on psychomotor performance and cognitive behavior and one trial did not show a beneficial effect on immunological parameters. So the evidences for an effect of ginseng on the mentioned indications were still in 1999 contradictive and the authors came to the conclusion that more rigorous investigations were needed to assess the possible efficacy of ginseng.

The aim of the present review was to collect and report the results of more recent clinical trials of ginseng (*Panax* species). The review should allow identification of possible interesting results or indications that deserve further investigation in the future.
All identified, preferentially randomized, placebo-controlled and blinded, clinical studies of the use of *Panax* species for any indication, from the late 1990s to early 2005 were included. In some areas, interesting results of *in vitro* or *in vivo* animal studies were furthermore included.

Physical and psychological functions

Some of the most investigated areas of the effects of ginseng are the influence on physical and psychological functions including effects on cognitive behavior, mood, quality of life, prevention of stress and general diseases and recovery from physical exercise.

Cognitive performance and mood
Several studies using animal models have shown improvement of cognitive functions like learning and memory after treatment with ginseng (Nishijo et al., 2004; Petkov et al., 2003). Human studies of the effects on cognitive performance have yielded contradictory results.

In a randomized double-blind study employing 112 healthy subjects above 40 years of age, no significant difference in the results of psychomotor, attention, learning and memory tests, measured before and after 8-9 weeks treatment with either placebo or 400 mg ginseng tablets (Gerimax Ginseng Extract, Dansk Droge A/S, Ishøj,

Denmark. Purity and content of ginseng not reported), were observed (Sørensen and Sonne, 1996). The ginseng group did show a tendency to better abstract thinking and faster reaction times than the placebo group but the results were not significant.

In a double-blind, placebo-controlled randomized, crossover study employing 20 healthy subjects the effect of a single dose of either 0 (placebo), 200, 400 or 600 mg ginseng extract (G115, Pharmaton SA, standardized to contain 4% triterpenoid glycosides/100 mg) on accuracy and responses were measured (Scholey and Kennedy, 2002). There was a washout period of 7 days between each treatment/study day. Scores on two computerized subtraction tasks were assessed pre-dosing and at 1, 2.5, 4 and 6 hours after dosing. 200 mg ginseng significantly slowed responses at all time points post-dosing compared to placebo, but it also significantly improved the accuracy at 4 h after dosing. 400 mg ginseng significantly improved accuracy at 4 and 6 h time points post-dosing. The crossover design of this study allowed each subject to be his or her own control. This controls for any possible interindividual variability that may influence the measured parameters. On the other hand it can be that the washout period not was long enough, which would lead to carryover effects in study courses where treatment consisted of ginseng during the first, second and/or third visit.
In another randomized placebo-controlled, double-blind study, administering a single dose of 400 mg *P. ginseng* extract (G115, Pharmaton) to 20 healthy subjects, improvement of memory, speed and accuracy in different cognitive performance tests were observed (Kennedy et al., 2002). Following a baseline cognitive assessment, further test sessions took place 1, 2.5, 4, and 6 h after the day's treatment was taken. The most striking effect in the study was the improvement in memory performance following ginseng treatment. Ginseng treatment did not significantly affect mood measured with Bond-Lader visual analogue scales.

A very recent study performed by the same group as the two previously mentioned studies, yielded similar results (Kennedy et al., 2004). This was a double-blind, placebo-controlled study employing 28 healthy subjects. The effect of a single dose of 200 mg ginseng extract (G115) on subjective mood and cognitive performance, measured pre-dosing and at 1, 2.5, 4 and 6 hours after dosing, was investigated. In comparison to placebo, ginseng improved the performance in several of the cognitive performance tests throughout the day. No significant improvement of mood was observed.

In contradiction to these three studies showing improved cognitive performance after a single dose of ginseng (G115), another recent study found no difference in the scores of several memory tests, between a group of subjects who had been taking ginseng supplement (brand or types not reported) for 2 years or more (n=86) compared to age- and education-matched control groups who had been either taking no supplements (n=86) or had been taking vitamin supplements only (n=86) (the latter group was included to control for possible effects based on general health awareness) (Persson et al., 2004).

A double-blind, randomized study has assessed the effects of Gericomplex (containing 40 mg ginseng extract G115, vitamins, minerals and trace elements) twice daily for 12 weeks, on quality of life and mood. A group of 205 healthy, employed subjects receiving the ginseng complex were compared to 185 healthy, employed subjects who received placebo. Significantly improved alertness, relaxation, appetite and overall score were observed after ginseng complex treatment (Wiklund et al., 1994). In a subgroup of the subjects with the 20% lowest score at baseline, the ginseng complex improved both vitality and depressed mood, indicating that subjects with poorest quality of life benefited the most from the ginseng treatment.

Another randomized placebo-controlled, double-blind clinical trial aimed to examine the possible effects of ginseng on mood as well (Cardinal and Engels, 2001). Eighty-three healthy young adults were randomly assigned to receive placebo, 200 mg or 400 mg ginseng capsules (*Panax ginseng* C.A. Meyer concentrate G115, Pharmaton Ltd, Lugano, Switzerland) for 60 days. Positive affect, negative affect and total mood disturbance were measured using different scaling tests, before and after the ginseng/placebo-intervention. No significant effects of ginseng were observed on positive affect, negative affect or total mood disturbance.

To assess the time-dependent effects of *Panax ginseng* on health-related quality of life (HRQOL) by use of a general health status questionnaire, 30 healthy young subjects were randomized in a double-blind manner to *P. ginseng* 200 mg/day (Ginsana) (n = 15) or matching placebo (n = 15) for 8 weeks (Ellis and Reddy, 2002). The Short Form-36 Health Survey version 2 (SF-36v2), a validated general health status questionnaire, was used to assess HRQOL at baseline and after 4 and 8 weeks of treatment. There were no significant differences in baseline demographics and baseline SF-36v2 scores between the groups. After 4 weeks of therapy, slightly higher scores in social functioning (*P. ginseng* 54.9+/-4.6 vs. placebo 49.2+/-6.5; $P = 0.014$), mental health (*P. ginseng* 52.2+/-7.7 vs. placebo 47.2+/-7.3; $P = 0.075$), and the mental component summary (*P. ginseng* 51.3+/-7.4 vs. placebo 44.3+/-8.3; $P = 0.019$) scales were observed in subjects randomized to *P. ginseng*. These differences did not persist to the 8-week time point. The incidence of adverse effects was 33% in the *P. ginseng* group compared with 17% in the placebo group ($P = 0.40$). Subjects given *P. ginseng* (58%) were more likely to state that they received active therapy than subjects given placebo (17%; $P < 0.05$) and they were significantly more likely to state that they felt differently during treatment.

Physical performance

Recent studies of the ability of ginseng to improve physical performance have not found evidence of any increase of for example maximal exercise capacity or positive influences on hormonal indices of stress during exercise. Only a single study has found improvement of different pulmonary function tests and Maximal Oxygen Consumption after ginseng treatment in patients with moderately-severe Chronic Obstructive Pulmonary Disease (Gross et al., 2002).

In a placebo-controlled, double-blind clinical trial, thirty-one healthy young men were randomly assigned to receive placebo (n=10), 200 mg (n=11) or 400 mg (n=10) ginseng capsules (*Panax ginseng* C.A. Meyer concentrate G115, Pharmaton Ltd, Lugano, Switzerland) for 60 days (Engels and Wirth, 1997). Submaximal and maximal aerobic exercise responses were measured before and after the intervention. Ginseng supplementation had no significant effect on oxygen consumption, respiratory exchange ratio, minute ventilation, blood lactic acid concentration or heart rate.

Another group studied the effect of a commercially manufactured standardized 200 mg dosage of 7% *Panax ginseng* for 21 days on peak aerobic exercise performance (Allen et al., 1998). Twenty young men and eight young women were randomly assigned to ginseng (n=13) or placebo (n=15) treatment in a double-blind design. Physical performance (symptom limited graded exercise test) on an ergometer was measured prior to and following treatment. No significant effect of ginseng treatment was observed for oxygen uptake, exercise time, workload, plasma lactate or hematocrit at peak levels, or for heart rate.

A randomized placebo-controlled clinical trial assessed the effects of *Panax ginseng* (4 mL 60% ethanolic *P. ginseng* extract, equivalent to 2 g/day of dried root, Mediherb Pty. Ltd., Warwick Queensland, Australia, diluted with 4 mL distilled water) for six weeks on competitive club-level endurance athletes engaged in their normal training (Gaffney et al., 2001). Sample size in this study was rather small as only 6 of the subjects receiving ginseng and 6 of those receiving placebo, completed the study. Before and after the interventions different measures of stress response (cortisol, testosterone, testosterone to cortisol ratio) and selected markers of the immune system status (circulating T-cells, T-helper cells (CD4), T-suppressor cells (CD8), CD4 to CD8 ratio, natural killer cells and B lymphocytes) were measured. Neither the immune system variables nor the endocrine components were changed significantly nor showed any clear trend from pre to post test in any of the two treatment groups (Gaffney et al., 2001).

To evaluate the effects of ginseng extract (G115) on Pulmonary Function Tests (PFTs), Maximum Voluntary Ventilation (MVV), Maximum Inspiratory Pressure (MIP) and Maximal Oxygen Consumption (VO_{2max}), 92 patients with moderately-severe Chronic Obstructive Pulmonary Disease (COPD) were randomly divided in groups to receive G115 100 mg (Ginsana, Pharmaton Ltd, Lugano, Switzerland) twice daily for three months (n = 49) or placebo (n = 43) (Gross et al., 2002). PFTs, MVV and MIP were studied before treatment and every two weeks for the 3-month-study period. Exercise test and VO_{2max} measurements were performed before the beginning and after six weeks and three months. Baseline demographics and pulmonary parameters were similar between the groups. In the ginseng, but not in the placebo group, all parameters significantly increased above baseline and compared with the placebo group. No side effects were observed. It was concluded that G115 100 mg twice daily for three months, but not placebo, improved PFTs, MVV, MIP and

VO_{2max} in patients with moderately-severe COPD.

In another randomized placebo-controlled, double-blind clinical trial, twenty-seven healthy young men supplemented their diet with placebo (n=12) or 400 mg (n=15) ginseng capsules (*Panax ginseng* C.A. Meyer concentrate G115, Pharmaton Ltd, Lugano, Switzerland equivalent to 2 g *P. ginseng* C.A. Meyer root material) for 60 days (Engels et al., 2003). The aims of the study were to examine the effects of prolonged ginseng supplements on secretory immunoglobin A (SIgA), physical performance and recovery responses of individuals undergoing exhausting interval exercise. SIgA is the primary immunoglobin contained in secretions of the mucosal immune system, and its levels in salivary fluids correlate more closely with resistance to respiratory infections caused by certain viruses, than do serum antibodies or other immune parameters (Engels et al., 2003). Before and after ginseng or placebo intervention each subject performed three 30-second Wingate tests interspersed with 3-minutes recovery periods. SIgA secretion rate, peak and mean mechanical power output and exercise recovery heart rate was determined. Postintervention minus preintervention change scores for SIgA secretion rate, exercise performance and recovery heart rate were similar between ginseng- and placebo-treated groups (P>0.05) (Engels et al., 2003).

Menopausal symptoms

Very few studies of the effects of ginseng on menopausal symptoms have been performed. Because ginseng have been reported to have estrogenic effects (Cho et al., 2004) and because positive effects on stress and mood furthermore have been stated, possible positive effects in postmenopausal women have been speculated. But also in this area a bit contradictory results have been obtained.

The effects of 6 g Korean red ginseng (the root of *Panax ginseng* C.A. Meyer) daily for 30 days, on the degree of psychological dysfunction and levels of stress hormones, were measured in 12 postmenopausal women with climacteric syndromes (Tode et al., 1999) and the levels were compared to the levels of 8 postmenopausal women without any climacteric syndromes, who were not treated. Ginseng treatment decreased the scores of psychological tests to normal range and significantly decreased the cortisol to dehydroepiandrosterone-sulfate ratio, which are stress-related hormones thought to be of importance for psychological functions such as depression and memory dysfunction in postmenopausal women (Tode et al., 1999). The study had several limitations, which should be recognized; it was not randomized, blinded or placebo-controlled. Furthermore was the sample size very small and the supplier of the ginseng used was not stated.

A randomized, multicenter, double-blind study assessed the effects of 200 mg standardized ginseng extract (Ginsana,

G115, GLP Ginsana Products SA, Lugano, Switzerland) compared with those of a placebo on quality of life and physiological parameters in 384 symptomatic postmenopausal women (Wiklund et al., 1999). Validated questionnaires (Psychological General Well-Being (PGWB) index, Women's Health Questionnaire (WHQ)) and Visual Analogue (VA) scales were used to assess the quality of life at baseline and after 16 weeks' treatment with either the ginseng extract or placebo. The efficacy of ginseng on postmenopausal symptoms, physiological parameters (follicle-stimulating hormone (FSH) and estradiol levels, endometrial thickness, maturity index and vaginal pH) was recorded at the same time points. Of the 384 randomized patients (mean age 53.5 +/- 4.0 years), the questionnaires were completed by 193 women treated with ginseng and 191 treated with placebo. The group treated with ginseng showed only a tendency for a slightly better overall symptomatic relief ($P< 0.1$). Exploratory analysis of PGWB subsets, however, reported P-values < 0.05 for depression, well-being and health subscales in favor of ginseng compared with placebo. No statistically significant effects were seen for the WHQ and the VA scales or the physiological parameters, including vasomotor symptoms (hot flushes).

In a double-blind, placebo-controlled study, post-menopausal women aged 51-66 were randomly assigned to 12 weeks' treatment with Gincosan (320 mg/day, Pharmaton SA, Switzerland, containing 120 mg Ginkgo biloba (GK501), and 200 mg *Panax ginseng* (G115)) (n=30), or matched placebo (n=27) (Hartley et al., 2004). They were given measurements of mood, somatic anxiety, sleepiness, and menopausal symptoms and a battery of cognitive tests before treatment and after 6 and 12 weeks of treatment. There were no significant effects of Gincosan treatment on ratings of mood, bodily symptoms of somatic anxiety, menopausal symptoms, or sleepiness or on any of the cognitive measures of attention, memory or frontal lobe function.

Diabetes

In the recent years several clinical studies have shown positive effects of ginseng on blood glucose levels both in diabetic patients and healthy individuals. One study was published in 1995 (Sotaniemi et al., 1995) and this study was included in the review by Vogler et al. from 1999 (Vogler et al., 1999). As mentioned in the introduction this group found reduction in fasting blood glucose levels in 24 newly diagnosed type 2 diabetic patients after 8 weeks treatment with 100 mg or 200 mg ginseng (Dansk Droge, Copenhagen) compared with 12 patients taking placebo. The study was double-blinded and randomized. The ginseng therapies furthermore elevated mood and improved psychophysical performance. The 200-mg dose of ginseng in addition to this significantly improved glycated hemoglobin (HbA_{1c}) and serum aminoterminalpropeptide (PIIINP). After publication of this study several clinical studies on the effects of ginseng treatment on blood glucose levels have been performed by a group of Canadian

researchers from St. Michael`s Hospital in Toronto:

Ten nondiabetic individuals were randomized to on 12 separate occasions receive a single dose of 0 (placebo), 3, 6 or 9 g of ground American ginseng root (*Panax quinquefolius L.*) at 40, 80, or 120 minutes before a 25 g oral glucose challenge (Vuksan et al., 2000a). Capillary blood glucose was measured prior to ingestion of ginseng or placebo capsules and at 0, 15, 30, 45, 60 and 90 minutes from start of challenge. Compared with the placebo, 3, 6 and 9 g of ginseng reduced (P<0.05) postprandial incremental glucose at 30, 45 and 60 minutes; also, 3 and 9 g of ginseng did so at 90 minutes. The 9 g ginseng dose administred 60 minutes before the glucose challenge, reduced incremental postprandial glucose relative to 3 g of ginseng (P<0.05). All ginseng doses reduced (P<0.05) area under the incremental glucose curve (3 g, 26.6%; 6 g, 29.3%; 9 g, 38.5%). Ginseng taken at different times did not have an additional influence on postprandial glycemia. The authors conclude that in nondiabetic individuals, 3, 6 or 9 g of American ginseng taken 40, 80 or 120 minutes before a glucose challenge similarly improved glucose tolerance.

In another study 10 nondiabetic subjects and 9 subjects with type 2 diabetes mellitus were randomized, on 4 separate occasions with minimum one weeks washout between each visit, to receiving 3 g American ginseng (*Panax quinquefolius L.*) or placebo capsules, either 40 minutes before or together with a 25-g oral glucose challenge (Vuksan et al., 2000b). A capillary blood sample was taken fasting and then at 15, 30, 45, 60, 90, and 120 (only for subjects with type 2 diabetes mellitus) minutes after the glucose challenge. In nondiabetic subjects, no differences were found in postprandial glycemia between placebo and ginseng when administered together with the glucose challenge. When ginseng was taken 40 minutes before the glucose challenge, significant reductions in area under the glycemic curve (18%+/-31%) were observed (P<0.05). In subjects with type 2 diabetes mellitus, significant reductions in area under the glycemic curve were observed both when ginseng was taken 40 minutes before (19%+/-22%) and together (22%+/-17%) with the glucose challenge (P<0.05).
In a similar study were ten type 2 diabetic patients (6 men, 4 women) randomly administered 0 g (placebo) or 3, 6, or 9 g ground American ginseng (*Panax quinquefolius L.*) root in capsules (Ontario-grown ground root of American ginseng, Chai-Na-Ta Corp., British Columbia, Canada) at 120, 80, 40, or 0 min before a 25-g oral glucose challenge (Vuksan et al., 2000c). Capillary blood glucose was measured before ingestion of ginseng or placebo and at 0, 15, 30, 45, 60, 90, and 120 min from the start of the glucose challenge. Two-way analysis of variance (ANOVA) demonstrated that treatment (3, 6, and 9 g ginseng) but not time of administration (120, 80, 40, or 0 min before the challenge) significantly affected postprandial glycemia (PPG) (P<0.05), with significant (P = 0.037) interaction for area under the curve (AUC). Pairwise comparisons showed that compared with 0 g (placebo), 3, 6, or 9 g significantly (P<0.05) reduced AUC (19.7%, 15.3%, and 15.9%, respectively) and incremental glycemia at 30 min (16.3%, 18.4%, and 18.4%, respectively), 45 min

(12.5%, 14.3%, and 14.3%, respectively), and 120 min (59.1%, 40.9%, and 45.5%, respectively). However, pairwise comparisons showed no differences between the 3-, 6-, or 9-g doses and any of the times of administration. Ginseng reduced PPG irrespective of dose and time of administration. No more than 3 g ginseng was required at any time in relation to the challenge to achieve reductions in postprandial glycemia.

In another randomized placebo-controlled, single-blinded, crossover study, 12 healthy subjects (7 men and 5 women) received 16 treatments: 0 (placebo), 1, 2, or 3 g American ginseng (*Panax quinquefolius L.* 3-year-old Ontario dried and ground ginseng root provided by Chai-Na-Ta Corp., Langley, Canada) at 40, 20, 10, or 0 min before a 25-g oral glucose challenge (Vuksan et al., 2001a). A minimum of 3 days separated each visit to minimize carryover effects. Capillary blood was collected before administration and at 0, 15, 30, 45, 60, and 90 min after the start of the glucose challenge. Postprandial glycemia was lower over the last 45 min of the test after doses of 1, 2, or 3 g ginseng than after placebo ($P < 0.05$); there were no significant differences between doses. The reductions in the areas under the curve for these 3 doses were 14.4% +/- 6.5%, 10.6% +/- 4.0%, and 9.1% +/- 6%, respectively. Glycemia in the last hour of the test and area under the curve were significantly lower when ginseng was administered 40 min before the challenge than when it was administered 20, 10, or 0 min before the challenge ($P < 0.05$). The authors conclude that American ginseng reduced postprandial glycemia in subjects without diabetes. These reductions were time dependent but not dose dependent: an effect was seen only when the ginseng was administered 40 min before the challenge. Doses within the range of 1-3 g were equally effective.

In a review from 2001 by the same Canadian group, a long-term study that apparently has only been published as an abstract (American Diabetes Association Annual Meeting, Diabetes Suppl (1) A95, Abstract No. 384, 2000), is summarized (Vuksan et al., 2001b). In this study 24 well-controlled type 2 diabetic subjects were randomized to consume 1 g of a standardized American ginseng extract (*Panax quinquefolius L.* CNT 2000 produced by Chai-Na-Tai Corp., Langley, BC, Canada) or placebo before each meal three times daily for 8 weeks while following Canadian Diabetes Association diet. 17 of the subjects maintained antidiabetic pharmacological treatment and 15 of the subjects maintained antihypertensive pharmacological treatment. Eight weeks of ginseng treatment modestly but significantly reduced HbA_{1c}, significantly decreased fasting blood glucose ($P<0.027$), nonsignificantly increased insulin levels and significantly decreased blood pressure compared to placebo treatment. It was concluded that American ginseng extract added to the conventional treatment of diabetes significantly improved glycaemic and blood pressure control beyond conventional treatment alone. Furthermore is a mechanism of action underlying American ginsengs hypoglycemic action proposed to be an enhancement of insulin secretion (Vuksan et al., 2001b).

Another study by the Canadian group was using a randomized, single-blind design. 12 healthy subjects (six males and six females) received 6 g American ginseng (*Panax quinquefolius L.* provided by Chai-Na-Ta Corp., BC, Canada) or placebo 40 min before a 75 g oral glucose tolerance test (Sievenpiper et al., 2003a). The protocol followed the guidelines for the oral glucose tolerance test, with venous blood samples drawn at -40, 0, 15, 30, 45, 60, 90 and 120 min. Ginsenosides in the ginseng were assessed by established methods for HPLC-UV. Repeated measures analysis of variance demonstrated that there was no significant effect of the ginseng on incremental plasma glucose (PG) or insulin (PI) or their areas under the curve. Indices of insulin sensitivity and release calculated from the oral glucose tolerance test were also unaffected. The ginseng contained 1.66% total ginsenosides, 0.90% (20S)-protopanaxadiol (PPD) ginsenosides, and 0.75% (20S)-protopanaxatriol (PPT) ginsenosides, with the following key ratios: PPD:PPT of 1.2, Rb(1):Rg(1) of 8.1, and Rb(2):Rc of 0.18. It was concluded that the used batch of ginseng was unable to reproduce the postprandial hypoglycemic effects that had been observed by the group previously. Possible explanations for this discrepancy was stated to be decrements in total ginsenosides and the key ratios PPD:PPT, Rb(1):Rg(1), and Rb(2):Rc. The authors conclude that the data suggest that the ginsenoside profile of American ginseng might play a role in its hypoglycemic effects, but that the involvement of other components cannot be excluded. It should be noted that opposed to previous studies conducted by this group, the oral glucose tolerance test used persist of 75 g glucose compared to 25 g used earlier.

The aim of one more study was to investigate whether *Panax ginseng* C.A. Meyer (three-year-old powdered whole root from Korean Ministry of Agriculture and Forestry, Seoul South Korea) was able to replicate the glycemia-lowering efficacy reported earlier for a batch of American ginseng (*Panax quinquefolius L.*) (Sievenpiper et al., 2003b). Two separate acute dose escalation studies were performed. Each study was conducted in a separate sample of 11 healthy subjects using a randomized, single-blind, placebo-controlled, multiple-crossover design. Treatments consisted of 0 (placebo), 1, 2, and 3 g of *P. ginseng* for the first study and 0 (placebo), 3, 6, and 9 g *P. ginseng* for the second study administered 40 minutes before a 75 g oral glucose tolerance test protocol with blood drawn at -40, 0, 15, 30, 45, 60, 90, and 120 minutes. A minimum of three days separated each visit to minimize carry-over effects. Ginsenoside content was analyzed by HPLC-UV. Neither the main effect of pooled-treatment, nor dose, nor either factors interaction with time was significant for incremental plasma glucose and insulin. But the diagnostically and therapeutically relevant two-hour plasma glucose value was significantly higher for pooled *P. ginseng* treatment than placebo (5.46 +/- 0.31 versus 4.99 +/- 0.30 mmol/L, $P = 0.050$). Ginsenoside analyses showed that the *P. ginseng* contained up to 96% lower and sevenfold higher quantities of various ginsenosides and their ratios than the previous efficacious batch of American ginseng. It was concluded that *P. ginseng* showed both null and opposing effects on

indices of acute postprandial plasma glucose and insulin. This was in contrast to previous findings with American ginseng. One explanation may be the marked ginsenoside differences. Also in this study a 75 g oral glucose tolerance test was used but it was noted in the discussion that 6 g of the original batch of American ginseng lowered the plasma glucose response to a 75 g oral glucose tolerance test significantly ($P < 0.05$) in 8 nondiabetic subjects, but published data from the study (presumably from 1991) could not be found.

The aim of yet another study by the Canadian group was to assess the effect of eight popular ginseng types on postprandial plasma glucose (PG) and insulin (PI) indices and to link the possible effects to ginsenoside profiles. Using a double-blind, randomized, multiple-crossover design, 12 healthy participants (6 females and 6 males) received a total of ten 3 g treatments, consisting of: American (*Panax quinquefolius* L.), American-wild (wild *Panax quinquefolius* L.), Korean (*Panax ginseng* C.A. Meyer), Korean-red (steam treated *Panax ginseng* C.A. Meyer), Vietnamese-wild (*Panax vietnemensis*), Siberian (*Eleutherococcus senticus*), Japanese-rhizome (*Panax japonicus* C.A. Meyer), and Sanchi (*Panax notoginseng* [Burk.] F.H. Chen) ginsengs and two placebos (Sievenpiper et al., 2004). Each treatment was given 40-minutes before a 75 g oral glucose tolerance test with blood drawn at -40, 0, 15, 30, 45, 60, 90, 120-minutes. HPLC-UV analysis quantified seven principal ginsenosides. Comparisons with placebo showed a tendency for American ginseng and Vietnamese ginseng to lower 90-min-PG ($P < 0.06$), while Korean ginseng raised peak-PG and AUC-PG, American-wild ginseng raised 120-min-PG, and Siberian ginseng raised 90-min-PG, 120-min-PG, and AUC-PG ($P < 0.05$). The different glycemic effects of the different types of ginseng could however not be predicted wholly by differences in their seven principal ginsenosides. Other unmeasured ginsenosides or non-ginsenoside components may as well have been involved.

Lung infections

The major cause of morbidity and mortality in cystic fibrosis patients is chronic *Pseudomonas aeruginosa* lung infection. Rat and mouse models of *Pseudomonas aeruginosa* lung infection mimicking that in patients with cystic fibrosis, treated with *Panax ginseng* C.A. Meyer (Song et al., 1997; Song et al., 1998; Song et al., 2002; Song et al., 2003) have shown significantly milder lung pathology and modulations of the immune system, which may favor faster clearance of the bacterial infection compared to saline treated control groups.

Only one publication of the ability of American ginseng (*Panax quinquefolius* L.) to prevent acute respiratory illness (ARI) in institutional settings including a nursing home and assisted living at three sites, has been found (McElhaney et al., 2004). It describes two randomized, double-blind, placebo-controlled trials conducted late in the 2000 (8 week) and 2000-2001 (12 week) influenza seasons. The participants were eighty-nine (2000) and 109 (2000-2001)

subjects, average age 81 and 83.5, respectively; 74% women. Approximately 90% had received influenza vaccine. Ginseng extract (CVT-E002), 200 mg or placebo was administered orally twice a day. Acute respiratory illness was defined as two new respiratory symptoms or one with a constitutional symptom. Confirmation of viral acute respiratory illness was done by culture (influenza or respiratory syncytial virus (RSV)) or serology for influenza. An intent-to-treat analysis of pooled data corrected for drug exposure time showed that the incidence of laboratory-confirmed influenza illness (LCII) was greater in placebo- (7 cases/101 subjects) than ginseng-treated (1/97) groups (odds ratio (OR)=7.73, *P*=0.033). Combined data for LCII and RSV illness were also greater in placebo- (9/101) than ginseng-treated (1/97) groups (OR=10.50, *P*=0.009). An overall 89% relative risk reduction of acute respiratory illness in the ginseng treated groups was found. A bias in these studies could be that 90% had received influenza vaccine.

Cancer

A prospective cohort study was conducted in Kangwha-eup from August 1987 to December 1992 to evaluate the preventive effect of ginseng against cancer on a population residing in a ginseng cultivation area (Yun and Choi, 1998). 4634 people over 40 years of age, who completed a questionnaire on ginseng intake, were included. In an attempt to obtain detailed information about ginseng intake, they were asked to specify their age at initial intake, frequency and duration of ginseng intake, the kind of ginseng, etc. Multiple logistic regression was used to estimate relative risks (RR) when controlling simultaneously for covariates. Ginseng consumers had a decreased risk (RR = 0.40, 95% confidence interval [CI]: 0.28-0.56) for developing cancer compared with non-consumers. On the type of ginseng, the RR was 0.31 (95% CI: 0.13-0.74) for fresh ginseng extract consumers and 0.34 (95% CI: 0.20-0.53) for consumers of multiple combinations. There was no cancer death among 24 red ginseng consumers. There was a decreased risk with a rise in the frequency of ginseng intake, showing a dose-response relationship. The RR of ginseng consumers were 0.33 (95% CI: 0.18-0.57) in gastric cancer and 0.30 (95% CI: 0.14-0.65) in lung cancer. Among ginseng preparations, fresh ginseng extract consumers were significantly associated with a decreased risk of gastric cancer (RR = 0.33, 95% CI: 0.12-0.88). The authors conclude that the results strongly suggest that *Panax ginseng* C.A. Meyer has non-organ specific preventive effect against cancer.

In a randomized, placebo-controlled clinical trial red ginseng powder from *Panax ginseng* C.A. Meyer was shown to inhibit the recurrence of stage III gastric cancer and to show immunomodulatory activities during postoperative chemotherapy, after a curative resection with D2 lymph node dissection (Suh et al., 2002). 42 patients were randomized to take 4.5 g ginseng per day or matched placebo during the first six months after operation. Flow cytometric analyses for peripheral T-lymphocyte subsets showed that ginseng restored CD4

levels to the initial preoperative values during postoperative chemotherapy. Depression of CD3 during postoperative chemotherapy was also inhibited by ginseng ingestion. The study demonstrated a five-year disease free survival and overall survival rate that was significantly higher in patients taking the red ginseng powder during postoperative chemotherapy versus control (68.2% versus 33.3%, 76.4% versus 38.5%, respectively, $P < 0.05$).

Hypertension

A single-blinded placebo-controlled study aimed to investigate the changes of diurnal blood pressure pattern after 8 weeks of red ginseng medication (4.5 g/day, Ginseng Radix Rubra, Korean Tobacco & Ginseng Corporation, Taejeon, Korea. 1.5 g three times a day) by 24-hour ambulatory blood pressure monitoring (every 30 minutes from 8 A.M. to 8 A.M. the following morning) (Han et al., 1998). 34 subjects were classified to 4 subgroups based on 24 hour ambulatory blood pressure monitoring. Placebo was administered for 4 weeks and red ginseng for the following 8 weeks. 24-hour ambulatory blood pressure monitoring was done 1) before starting the intervention, 2) after 4 weeks of placebo administration and 3) after further 8 weeks ginseng administration. In 26 subjects with essential hypertension, 24 hour mean systolic blood pressure decreased significantly ($P = 0.03$) while diastolic blood pressure only showed a tendency of decline. The decreases in pressures were observed at daytime (8 A.M.-6 P.M.) and dawn (5 A.M.-7 A.M.). In 8 subjects with white coat hypertension, no significant blood pressure change was observed. The authors suggest that red ginseng might be useful as a relatively safe medication adjuvant to current antihypertensive medications.

The effect of 4.5 g Korean red ginseng per day for approximately 24 months, on vascular endothelial cell dysfunction in patients with hypertension has been investigated in a randomized clinical trial (Sung et al., 2000). Seventeen patients with hypertension were divided into a ginseng-treated (7) and a non-treated (10) group and 10 healthy subjects were included as control group. The ginseng treatment period was approximately 24 months (ranging 21-27 months). To assess the function of the vascular endothelial cell, changes of forearm blood flow to infusion of acetylcholine, sodium nitroprusside and bradykinin in incremental doses, were measured by venous occlusion plethysmography. In the ginseng-treated hypertensive group, forearm bloods flows at the highest dose of acetylcholine and bradykinin, were significantly higher than those of the non-treated hypertensive group and were not different from those of the control group. In the case of sodium nitroprusside infusion, no significant differences were observed between the control, non-treated and treated groups. Based on these results it is speculated by the authors that Korean red ginseng can improve the vascular endothelial dysfunction in patients with hypertension through increasing the synthesis of nitric oxide.

Miscellaneous

The efficacy of Korean red ginseng for erectile dysfunction using the International Index of Erectile Function, RigiScan (UroHealth Systems, Laguna Niguel, California), hormonal levels and penile duplex ultrasonography with audiovisual sexual stimulation has also been investigated in a total of 45 patients with clinically diagnosed erectile dysfunction in a randomized, double-blind, placebo controlled, crossover study (8 weeks on treatment, 2 weeks of washout and 8 weeks on treatment) (Hong et al., 2002). The effects of Korean red ginseng and placebo were compared using multiple variables. The ginseng dose was 900 mg 3 times daily. Mean International Index of Erectile Function scores were significantly higher in patients treated with Korean red ginseng than in those who received placebo. Scores on questions 3 (penetration) and 4 (maintenance) were significantly higher in the ginseng than in the placebo group. In response to the global efficacy question 60% of the patients answered that Korean red ginseng improved erection. Among other variables penile tip rigidity on RigiScan showed significant improvement for ginseng versus placebo. The crossover design allowed each subject to be his own control. Washout period could be to short, which would lead to carryover effects in study courses where treatment consisted of ginseng during the first period; this would reduce the effect observed.

In a clinical study employing eight young male subjects the effects of *Panax ginseng* extract (2 g three times a day for 8 weeks) on lipid metabolism were examined by measuring cholesterol, malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) before and after intervention (Kim and Park, 2003). ILWha Co. Ltd., Kyonggi, Korea supplied the ginseng extract and financed the study. Ginseng was extracted with 50% of alcohol and the components were characterized as follows: 2.5% for R_{b1}, 2.1% for R_{b2}, 2.6% for R_c, 1.1% for R_d, 1.2% for R_e, 0.4% for R_{g1}, 35 for H_2O, 7% for protein, 0.3% for lipid, 3.5% for ash, 35% for sugar, 0.5% for amino acid, 0.2% for vitamin and 4% for others. Serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and plasma MDA levels were decreased by administration of ginseng, however high density lipoprotein (HDL) was increased. Those results suggest that a possible hypolipidemic effect of ginseng could be associated with a decrease in TC, TG, LDL, MDA levels and an increase in HDL. Administration of ginseng increased SOD and CAT activities. It should be noted that the used sample size (8) was very small and that the study not was placebo-controlled and blinded.

Drug interactions and effects on enzymes

In an *in vitro* study the effect of a standardized *Panax ginseng* extract (G115), a standardized *Panax quinquefolius* (or North American ginseng) extract (NAGE), and individual ginsenosides (Rb1, Rb2, Rc,

Rd, Re, Rf, and Rg1) on CYP1 catalytic activities, was assessed by measuring 7-ethoxyresorufin O-dealkylation (Chang et al., 2002). G115 and NAGE decreased human recombinant CYP1A1, CYP1A2, and CYP1B1 activities in a concentration-dependent manner. A striking finding was that NAGE was 45-fold more potent than G115 in inhibiting CYP1A2. Compared with G115, NAGE also preferentially inhibited 7-ethoxyresorufin O-dealkylation activity in human liver microsomes. Rb1, Rb2, Rc, Rd, Re, Rf, and Rg1, either individually or as a mixture and at the levels reflecting those found in an inhibitory concentration (100 μg/ml) of NAGE or G115, did not influence CYP1 activities. However, at a higher single ginsenoside concentration (50 μg/ml), Rb1, Rb2, Rc, Rd, and Rf inhibited these activities.

To investigate the possible effect of ginseng on the urinary excretion of the 6-beta-hydroxycortisol/cortisol ratio as a marker of cytochrome P450 (CYP) 3A enzyme induction, twenty subjects received *Panax ginseng* 100 mg standardized to 4% ginsenosides twice daily for 14 days (Anderson et al., 2003). *Panax ginseng* did not significantly alter the urinary 6-beta-OH-cortisol/cortisol ratio, suggesting that unlike St. John's wort, *P. ginseng* is not a CYP3A inducer.

In another *in vitro* study, ginsenoside Rb1, Rb2, Rc, and Rd (from Idofine Chemical Co. Sommerville, NJ) at various concentrations (0.1, 1, 10, 100, 200 μmol/L) were investigated for their inhibitory effects on hepatic CYP2C9 and CYP3A4 catalytic activities in human liver microsomes (He and Edeki, 2004). Tolbutamide 4-methylhydroxylation and testosterone 6-beta-hydroxylation were used as index reactions of CYP2C9 or CYP3A4 catalytic activities, respectively. The metabolites of both reactions were measured by high-performance liquid chromatography and used as indicators of whether enzymes were inhibited or unaffected by these agents. Ginsenoside Rd had significant inhibitory potency on both CYP2C9- and CYP3A4-mediated index reactions with IC(50) values of 105 and 62 μmol/L, respectively. Ginsenosides Rb1, Rb2, and Rc had limited inhibitory activities on both enzyme reaction systems. It is concluded by the authors that ginsenoside Rd have the potential to interact with conventional medicines that are metabolized by CYP2C9 and CYP3A4 *in vivo*.

P-glycoprotein (Pgp) is a 170 kDa phosphorylated glycoprotein encoded by human MDR1 gene. It is responsible for the systemic disposition of numerous structurally and pharmacologically unrelated lipophilic and amphipathic drugs, carcinogens, toxins, and other xenobiotics in many organs, such as the intestine, liver, kidney, and brain. By using an ATPase assay, purified Pgp protein or intact Pgp-expressing cells, and proper probe substrates, several ginsenosides have been found to be inhibitors of Pgp (Zhou et al., 2004). The inhibition of Pgp activity by these constituents of different ginseng species could result in altered absorption and bioavailability of drugs that are Pgp substrates.

To evaluate the interactions between American ginseng and warfarin, a randomized, double-blind, placebo-

controlled trial has been performed (Yuan et al., 2004). In a 4-week study, 20 young, healthy volunteers received warfarin for 3 days during weeks 1 and 4. Beginning in week 2, subjects were assigned to receive either American ginseng (*Panax quinquefolius*, 0.5 g powdered ground root. Using HPLC total ginsenoside content was 5.19%; Rb1 1.93%; Rb2 0.2%; Rc 0.61%; Rd 0.42%; Re 1.68%; Rg1 0.35%) or placebo. The peak International normalized ratio (prothrombin time test-control ratio) statistically significantly decreased after 2 weeks of ginseng administration compared with placebo (difference between ginseng and placebo, -0.19 [95% CI, -0.36 to -0.07]; $P = 0.0012$). The International normalized ratio area under the curve (AUC), peak plasma warfarin level, and warfarin AUC were also statistically significantly reduced in the ginseng group as compared with the placebo group. Peak International normalized ratio and peak plasma warfarin level were positively correlated. The authors conclude that American ginseng reduces the anticoagulant effect of warfarin. And when prescribing warfarin, physicians should ask patients about ginseng use.

The aim of another study was to investigate the effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin (Jiang et al., 2004). Warfarin is a racemic mixture of the R- and S-enantiomers. Most of the anticoagulant activity of warfarin is attributable to S-warfarin but the activity is as well influenced by the hepatic levels of vitamin K. CYP2C9 is the principal enzyme responsible for S-warfarin metabolism. The ginseng used in the study was the brand Golden Glow (Korean ginseng, each capsule containing extract equivalent to 0.5 g *Panax ginseng* root and 8.93 mg ginsenosides as ginsenoside Rg1). It was an open-label, three-way randomized crossover study in 12 healthy male subjects, who received a single 25-mg dose of warfarin alone or after 14 days pretreatment with St John's wort, or 7 days pretreatment with ginseng. Dosing with St John's wort or ginseng was continued for 7 days after administration of the warfarin dose. Platelet aggregation, international normalized ratio (INR) of prothrombin time, warfarin enantiomer protein binding, warfarin enantiomer concentrations in plasma and S-7-hydroxywarfarin concentration in urine were measured. INR and platelet aggregation were not affected by treatment with St John's wort or ginseng. The apparent clearances of S-warfarin after warfarin alone or with St John's wort or ginseng were, respectively, 198 +/- 38 ml h(-1), 270 +/- 44 ml h(-1) and 220 +/- 29 ml h(-1). The respective apparent clearances of R-warfarin were 110 +/- 25 ml h(-1), 142 +/- 29 ml h(-1) and 119 +/- 20 ml h(-1). St John's wort and ginseng did not affect the apparent volumes of distribution or protein binding of warfarin enantiomers. The authors conclude that St John's wort significantly induced the apparent clearance of both S-warfarin and R-warfarin, which in turn resulted in a significant reduction in the pharmacological effect of rac-warfarin. Coadministration of warfarin with ginseng did not affect the pharmacokinetics or pharmacodynamics of either S-warfarin or R-warfarin (Jiang et al., 2004).

Conclusions and possible future research areas

A total of 35 clinical studies were reviewed. Of these 23 studies showed a positive effect (or not a negative effect e.g. induction or interaction) of ginseng (*Panax* species) on one or more of the measured effect parameters and 12 studies showed no significant effect (or did show an ability to interact with warfarin). The design of the studies was of very different quality but most of them were randomized, placebo-controlled and blinded, and a few were cohort studies.

Eight studies investigating the possible effects of ginseng on cognitive performance and mood were included. Three studies showed improvement of cognitive performance tests, particularly improved accuracy and speed but with no effects on mood after a single dose of 400 or 200 mg G115, standardized ginseng extract. One study reported improved general health after G115 supplement twice daily for 12 weeks. One study showed improvement of health-related-quality of life after 4 weeks treatment with 200 mg G115 per day but after 8 weeks of treatment no significant difference compared to placebo was observed. Three studies showed no significant effects of long term ginseng supplement on memory tests or mood.

Five studies of the possible effects of *Panax ginseng* (three using G115) on physical performance was included. Only one of these showed positive effects of 100 mg G115 twice daily for three months, on several lung function tests in patients with chronic obstructive pulmonary disease. Two of three studies showed positive effects of ginseng supplement in women with menopausal symptoms.

Eight studies performed by a group of Canadian researchers, aimed to investigate the possible glucose lowering effect of ginseng. Six of these yielded positive results in favour of American ginseng (*Panax quinquefolius L.*) compared with placebo. Generally the positive effects observed were lower plasma glucose levels after a glucose challenge test in both healthy subjects and type 2 diabetic patients after a single dose of American ginseng. The opposite effect on plasma glucose were actually seen in one study after a single dose of *P. ginseng* and a specific batch of American ginseng did not have glucose lowering effect probably because of a lower or altered ginsenoside profile. One of the studies was a long-term study (8 weeks) and this study also found lower fasting blood glucose and reduced HbA_{1c} in type 2 diabetic patients after intake of American ginseng compared to intake of placebo before each meal.

Furthermore has two clinical studies shown reduced risk of acute respiratory illness during treatment with American ginseng, a cohort study has shown reduced risk of cancer when taking ginseng supplement and one randomized study has shown improved recovery after gastric cancer operation after ginseng treatment compared with placebo treatment. Treatment with Korean red ginseng has in two studies shown positive effects on blood pressure and endothelial function in hypertensive patients. Korean red ginseng has also been found to have

positive effects on male sexual dysfunction. And one study has indicated that *Panax ginseng* has positive effects on lipid metabolism.

In vitro studies have indicated that some ginsenosides may inhibit CYP2C9 and CYP3A4 and P-glycoprotein, and a clinical study has not found that ginseng treatment lead to an indiction of CYP3A4. One clinical study has shown interaction of American ginseng (*Panax quinquefolius*) with warfarin but another clinical study using *Panax ginseng* has not found interaction with warfarin.

This summary of areas in which positive effects of ginseng have been obtained, indicate that an obvious future research area is the use of American ginseng in the treatment of type 2 diabetes. It can be speculated that ginseng supplement could reduce the need for other diabetic medicines and postpone the point where insulin therapy is required in type 2 diabetic patients. Other possible areas where positive effects could be expected are cancer, lung infections and perhaps hypertension. It is very difficult to conclude about the effects of ginseng on cognitive functions because these functions are a bit more difficult to measure exactly, but several studies does indicate improved test scores and general health after ginseng treatment. But in all of the areas further studies are still needed to evaluate the possible positive effects of ginseng.

References

Allen,J.D., McLung,J., Nelson,A.G., and Welsch,M. (1998). Ginseng supplementation does not enhance healthy young adults' peak aerobic exercise performance. J. Am. Coll. Nutr. *17*, 462-466.

Anderson,G.D., Rosito,G., Mohustsy,M.A., and Elmer,G.W. (2003). Drug interaction potential of soy extract and Panax ginseng. J. Clin. Pharmacol. *43*, 643-648.

Bahrke,M.S. and Morgan,W.P. (2000). Evaluation of the ergogenic properties of ginseng. Sports Med. *29*, 113-133.

Cardinal,B.J. and Engels,H.J. (2001). Ginseng does not enhance psychological well-being in healthy, young adults: results of a double-blind, placebo-controlled, randomized clinical trial. J. Am. Diet. Assoc. *101*, 655-660.

Chang,T.K., Chen,J., and Benetton,S.A. (2002). In vitro effect of standardized ginseng extracts and individual ginsenosides on the catalytic activity of human CYP1A1, CYP1A2, and CYP1B1. Drug Metab. Dispos. *30*, 378-384.

Cho,J., Park,W., Lee,S., Ahn,W., and Lee,Y. (2004). Ginsenoside-Rb1 from Panax ginseng C.A. Meyer activates estrogen receptor-alpha and -beta, independent of ligand binding. J. Clin. Endocrinol. Metab. *89* , 3510-3515.

Cui,J., Garle,M., Eneroth,P., and Björkhem,I. (1994). What do commercial

ginseng preparations contain? The Lancet *344*, 134.

Dey,L., Xie,J.T., Wang,A., Wu,J., Malecar,S.A., and Yuan,C.S. (2003). Anti-hyperglycemic effects of ginseng: comparison between root and berry. Phytomedicine. *10*, 600-605.

Ellis,J.M. and Reddy,P. (2002). Effects of Panax ginseng on quality of life. Ann. Pharmacother. *36*, 375-379.

Engels,H.J., Fahlman,M.M., and Wirth,J.C. (2003). Effects of ginseng on secretory IgA, performance, and recovery from interval exercise. Med. Sci. Sports Exerc. *35*, 690-696.

Engels,H.J. and Wirth,J.C. (1997). No ergogenic effects of ginseng (Panax ginseng C.A. Meyer) during graded maximal aerobic exercise. J. Am. Diet. Assoc. *97*, 1110-1115.

Gaffney,B.T., Hugel,H.M., and Rich,P.A. (2001). The effects of Eleutherococcus senticosus and Panax ginseng on steroidal hormone indices of stress and lymphocyte subset numbers in endurance athletes. Life Sci. *70*, 431-442.

Gross,D., Shenkman,Z., Bleiberg,B., Dayan,M., Gittelson,M., and Efrat,R. (2002). Ginseng improves pulmonary functions and exercise capacity in patients with COPD. Monaldi. Arch. Chest Dis. *57*, 242-246.

Han,K.H., Choe,S.C., Kim,H.S., Sohn,D.W., Nam,K.Y., Oh,B.H., Lee,M.M., Park,Y.B., Choi,Y.S., Seo,J.D., and Lee,Y.W. (1998). Effect of red ginseng on blood pressure in patients with essential hypertension and white coat hypertension. Am. J. Chin. Med. *26*, 199-209.

Hartley,D.E., Elsabagh,S., and File,S.E. (2004). Gincosan (a combination of Ginkgo biloba and Panax ginseng): the effects on mood and cognition of 6 and 12 weeks' treatment in post-menopausal women. Nutr. Neurosci. *7*, 325-333.

He,N. and Edeki,T. (2004). The inhibitory effects of herbal components on CYP2C9 and CYP3A4 catalytic activities in human liver microsomes. Am. J. Ther. *11*, 206-212.

Hong,B., Ji,Y.H., Hong,J.H., Nam,K.Y., and Ahn,T.Y. (2002). A double-blind crossover study evaluating the efficacy of korean red ginseng in patients with erectile dysfunction: a preliminary report. J. Urol. *168*, 2070-2073.

Jiang,X., Williams,K.M., Liauw,W.S., Ammit,A.J., Roufogalis,B.D., Duke,C.C., Day,R.O., and McLachlan,A.J. (2004). Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br. J. Clin. Pharmacol. *57*, 592-599.

Kennedy,D.O., Haskell,C.F., Wesnes,K.A., and Scholey,A.B. (2004). Improved cognitive performance in human volunteers following administration of guarana (*Paullinia cupana*) extract: comparison and interaction with *Panax ginseng*. Pharmacol. Biochem. Behav. *79*, 401-411.

Kennedy,D.O., Scholey,A.B., and Wesnes,K.A. (2002). Modulation of cognition and mood following

administration of single doses of Ginkgo biloba, ginseng, and a ginkgo/ginseng combination to healthy young adults. Physiol. Behav. *75*, 739-751.

Kim,S.H. and Park,K.S. (2003). Effects of Panax ginseng extract on lipid metabolism in humans. Pharmacol. Res. *48*, 511-513.

Kim,W.Y., Kim,J.M., Han,S.B., Lee,S.K., Kim,N.D., Park,M.K., Kim,C.K., and Park,J.H. (2000). Steaming of ginseng at high temperature enhances biological activity. J. Nat. Prod. *63*, 1702-1704.

McElhaney,J.E., Gravenstein,S., Cole,S.K., Davidson,E., O'neill,D., Petitjean,S., Rumble,B., and Shan,J.J. (2004). A placebo-controlled trial of a proprietary extract of North American ginseng (CVT-E002) to prevent acute respiratory illness in institutionalized older adults. J. Am. Geriatr. Soc. *52*, 13-19.

Nishijo,H., Uwano,T., Zhong,Y.M., and Ono,T. (2004). Proof of the mysterious efficacy of ginseng: basic and clinical trials: effects of red ginseng on learning and memory deficits in an animal model of amnesia. J. Pharmacol. Sci. *95*, 145-152.

Persson,J., Bringlov,E., Nilsson,L.G., and Nyberg,L. (2004). The memory-enhancing effects of Ginseng and Ginkgo biloba in healthy volunteers. Psychopharmacology (Berl.) *172*, 430-434.

Petkov,V.D., Belcheva,S., and Petkov,V.V. (2003). Behavioral effects of Ginkgo biloba L., Panax ginseng C.A. Mey. and Gincosan. Am. J. Chin. Med. *31*, 841-855.

Scholey,A.B. and Kennedy,D.O. (2002). Acute, dose-dependent cognitive effects of Ginkgo biloba, Panax ginseng and their combination in healthy young volunteers: differential interactions with cognitive demand. Hum. Psychopharmacol. *17*, 35-44.

Shibata,S., Tanaka,O., Soma,K., and et al. (1965). Studies on saponins and sapogenins of ginseng: the structure of panaxatriol. Tetrahedron Lett *3*, 207-213.

Sievenpiper,J.L., Arnason,J.T., Leiter,L.A., and Vuksan,V. (2003b). Null and opposing effects of Asian ginseng (Panax ginseng C.A. Meyer) on acute glycemia: results of two acute dose escalation studies. J. Am. Coll. Nutr. *22*, 524-532.

Sievenpiper,J.L., Arnason,J.T., Leiter,L.A., and Vuksan,V. (2003a). Variable effects of American ginseng: a batch of American ginseng (*Panax quinquefolius L.*) with a depressed ginsenoside profile does not affect postprandial glycemia. Eur. J. Clin. Nutr. *57*, 243-248.

Sievenpiper,J.L., Arnason,J.T., Leiter,L.A., and Vuksan,V. (2004). Decreasing, null and increasing effects of eight popular types of ginseng on acute postprandial glycemic indices in healthy humans: the role of ginsenosides. J. Am. Coll. Nutr. *23*, 248-258.

Song,Z., Johansen,H.K., Faber,V., Moser,C., Kharazmi,A., Rygaard,J., and Hoiby,N. (1997). Ginseng treatment reduces bacterial load and lung pathology in chronic Pseudomonas aeruginosa pneumonia in rats. Antimicrob. Agents Chemother. *41*, 961-964.

Song,Z., Kharazmi,A., Wu,H., Faber,V., Moser,C., Krogh,H.K., Rygaard,J., and Hoiby,N. (1998). Effects of ginseng treatment on neutrophil chemiluminescence and immunoglobulin G subclasses in a rat model of chronic Pseudomonas aeruginosa pneumonia. Clin. Diagn. Lab. Immunol. *5*, 882-887.

Song,Z., Moser,C., Wu,H., Faber,V., Kharazmi,A., and Hoiby,N. (2003). Cytokine modulating effect of ginseng treatment in a mouse model of Pseudomonas aeruginosa lung infection. J. Cyst. Fibros. *2*, 112-119.

Song,Z., Wu,H., Mathee,K., Høibi,N., and Kharazmi,A. (2002). Gerimax ginseng regulates both humoral and cellular immunity during chronic *Pseudomonas aeruginosa* lung infection. The Journal of Alternative and Complementary Medicine *8*, 459-466.

Sotaniemi,E.A., Haapakoski,E., and Rautio,A. (1995). Ginseng therapy in non-insulin-dependent diabetic patients. Diabetes Care *18*, 1373-1375.

Suh,S., Krogh,M., Kim,N.R., Joh,Y.G., and Cho,M.Y. (2002). Effects of Red Ginseng Upon Postoperative Immunity and Survival in Patients with Stage III Gastric Cancer. American Journal of Chinese Medicine *30*, 483-494.

Sung,J., Han,K.H., Zo,J.H., Park,H.J., Kim,C.H., and Oh,B.H. (2000). Effects of red ginseng upon vascular endothelial function in patients with essential hypertension. Am. J. Chin. Med. *28*, 205-216.

Sørensen,H. and Sonne,J. (1996). A double-masked study of the effects of ginseng on cognitive functions. Current Therapeutic Research *57*, 959-968.

Tode,T., Kikuchi,Y., Hirata,J., Kita,T., Nakata,H., and Nagata,I. (1999). Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. Int. J. Gynaecol. Obstet. *67*, 174.

Vogler,B.K., Pittler,M.H., and Ernst,E. (1999). The efficacy of ginseng. A systematic review of randomised clinical trials. Eur. J. Clin. Pharmacol. *55*, 567-575.

Vuksan,V., Sievenpiper,J.L., Koo,V.Y., Francis,T., Beljan-Zdravkovic,U., Xu,Z., and Vidgen,E. (2000b). American ginseng (Panax quinquefolius L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. Arch. Intern. Med. *160*, 1009-1013.

Vuksan,V., Sievenpiper,J.L., Wong,J., Xu,Z., Beljan-Zdravkovic,U., Arnason,J.T., Assinewe,V., Stavro,M.P., Jenkins,A.L., Leiter,L.A., and Francis,T. (2001a). American ginseng (Panax quinquefolius L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals. Am. J. Clin. Nutr. *73*, 753-758.

Vuksan,V., Sievenpiper,J.L., Xu,Z., Wong,E.Y., Jenkins,A.L., Beljan-Zdravkovic,U., Leiter,L.A., Josse,R.G., and Stavro,M.P. (2001b). Konjac-Mannan and American ginsing: emerging alternative

therapies for type 2 diabetes mellitus. J. Am. Coll. Nutr. *20*, 370S-380S.

Vuksan,V., Stavro,M.P., Sievenpiper,J.L., Beljan-Zdravkovic,U., Leiter,L.A., Josse,R.G., and Xu,Z. (2000c). Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. Diabetes Care *23*, 1221-1226.

Vuksan,V., Stavro,M.P., Sievenpiper,J.L., Koo,V.Y., Wong,E., Beljan-Zdravkovic,U., Francis,T., Jenkins,A.L., Leiter,L.A., Josse,R.G., and Xu,Z. (2000a). American ginseng improves glycemia in individuals with normal glucose tolerance: effect of dose and time escalation. J. Am. Coll. Nutr. *19*, 738-744.

Wiklund,I.K., Karlberg,J., and Lund,B. (1994). A double-blind comparison of the effect on quality of life of a combination of vital substances including standardized ginseng G115 and placebo. Current Therapeutic Research *55*, 32-42.

Wiklund,I.K., Mattsson,L.A., Lindgren,R., and Limoni,C. (1999). Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group. Int. J. Clin. Pharmacol. Res. *19*, 89-99.

Xie,J.T., Aung,H.H., Wu,J.A., Attel,A.S., and Yuan,C.S. (2002). Effects of American ginseng berry extract on blood glucose levels in ob/ob mice. Am. J. Chin. Med. *30*, 187-194.

Xie,J.T., Mehendale,S.R., Wang,A., Han,A.H., Wu,J.A., Osinski,J., and Yuan,C.S. (2004a). American ginseng leaf: ginsenoside analysis and hypoglycemic activity. Pharmacol. Res. *49*, 113-117.

Xie,J.T., Wu,J.A., Mehendale,S., Aung,H.H., and Yuan,C.S. (2004b). Anti-hyperglycemic effect of the polysaccharides fraction from American ginseng berry extract in ob/ob mice. Phytomedicine. *11*, 182-187.

Yuan,C.S., Wei,G., Dey,L., Karrison,T., Nahlik,L., Maleckar,S., Kasza,K., Ang-Lee,M., and Moss,J. (2004). Brief communication: American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled Trial. Ann. Intern. Med. *141*, 23-27.

Yun,T.K. and Choi,S.Y. (1998). Non-organ specific cancer prevention of ginseng: a prospective study in Korea. International Journal of Epidemiology *27*, 359-364.

Zhou,S., Lim,L.Y., and Chowbay,B. (2004). Herbal modulation of P-glycoprotein. Drug Metab Rev *36*, 57-104.

Summary

Ginseng has been used as an herbal remedy in Asia for thousands of years and it has been claimed effective in improving several disorders and general health functions including cancer, diabetes, cardiovascular disorders, immune functions, vitality, sexual function, cognitive and physical performance. But early clinical trials (from before the mid 1990s) aimed to test the efficacy of ginseng used for any of the claimed indications have yielded contradictory results.

The aim of this review was to collect and report the results of more recent clinical trials of ginseng (Panax species). We would like the review to allow identification of any possible interesting results or indications that deserve further investigation in the future.

The review indicates that an obvious future research area is the use of American ginseng (Panax quinquefolius) in the treatment of diabetes. Other possible areas where positive effects could be expected are cancer, lung infections and perhaps hypertension. But further studies are still needed to evaluate the possible clinical effects of ginseng.

Plant production

Horticulture

Livestock

Grøn Viden is issued in separate horticulture, plant production and livestock farming series. For more information on our publications please visit our website www.agrsci.dk