



Clinical Research Review

e-Monitor No. 22 July 2008

by Michelle Morgan

Clinical Studies Evaluating Herbs

Prophylaxis of atherosclerosis in patients with metabolic syndrome: A phytotherapeutic approach.

Siegel G, Schafer P, Sauer F et al. *Z Phytother* 2008; **29**(S1): S16

A previous publication reported that administration of standardised Ginkgo extract reduced nano plaque formation and nano plaque size in cardiovascular high-risk patients who had undergone coronary bypass surgery (*Atherosclerosis* 2007; **192**(2): 438-444). (Nano plaques are considered to be the very first stage of degeneration of the arterial wall that leads to atherosclerosis and eventually heart disease.) The Ginkgo treatment also lowered lipoprotein(a) and the percentage of oxidised LDL (low density lipoprotein). (A high plasma level of lipoprotein(a) is associated with increased risk of atherosclerotic cardiovascular disease. Oxidised LDL promotes the build up and progression of plaques. See also e-Monitor No. 21 May 2008 pp 1-2.

These beneficial effects of Ginkgo were investigated in a second observational trial involving 11 patients with metabolic syndrome in the initial stage. After 2 months of treatment with standardised Ginkgo extract (240 mg/day, equivalent to 12 g/day of dried leaf), nano plaque formation and nano plaque size were reduced by 14.7% and 21.5% respectively. These results were highly statistically significant. Ginkgo lowered the percentage of oxidised LDL (by 21.0%), lowered lipoprotein(a) concentration (by 26.3%) and upregulated the activities of superoxidase dismutase and glutathione peroxidase (19.6%, 11.6% respectively).

An extensive range of other biomarkers were measured, which led the authors to conclude that the atherosclerosis-inhibiting effect of Ginkgo can be attributed to:

- a stimulation of radical scavenging enzymes in the body
- a restriction of the risk factors (lipoprotein(a), percentage of oxidised LDL)
- an increase in nitric oxide/cyclic GMP release (having a vasodilatory effect)

Interestingly, treatment with Ginkgo resulted in a significant increase in both the mean corpuscular haemoglobin and the mean corpuscular haemoglobin concentration. In conjunction with the observed vasodilation, this will result in improved oxygen supply combined with enhanced organ perfusion.

Key Finding: Standardised Ginkgo extract demonstrated potent antiatherosclerotic effects in metabolic syndrome.

Safety and efficacy of silymarin on patients with acute hepatitis: A randomized, controlled trial.

El-Kamary S, Shardell M, Metwally M et al. *Am J Trop Med Hyg* 2007; **77**(5, Suppl S): 210, Abstract No. 731

Clinical studies of the concentrated extract of St Mary's thistle (*Silybum marianum*), known as silymarin, for patients with acute or chronic viral hepatitis have shown inconclusive results. A randomised, double-blind, placebo-controlled trial in Egypt investigated treatment with silymarin in patients with acute hepatitis (regardless of aetiology) exhibiting serum alanine aminotransferase levels more than 2.5 times the upper limit of normal. Patients received silymarin (420 mg/day) or a multivitamin placebo for four weeks, and were assessed at week 2, week 4 and at the 4-week follow-up (i.e. week 8). These patients receiving silymarin had a significantly earlier improvement in biliary excretion (direct serum bilirubin, total serum bilirubin, scleral icterus, jaundice and dark urine). Improvement in parameters

associated with hepatic inflammation and systemic manifestations (such as fatigue and anorexia) were not significant. No serious adverse events were noted.

Key Finding: In patients with acute hepatitis of various causes, silymarin improved parameters reflecting biliary excretion.

Topical Calendula and betamethasone valerate in the prevention of acute radiation dermatitis: a randomized prospective trial.[In Persian]

Fotouhi M, Samee F, Hashemi FA et al. *Tehran Univ Med J* 2007; **65**(3): 23-29

Sixty breast cancer patients randomly received a moderately-potent steroid ointment (0.1% betamethasone) or 0.1% Calendula ointment. All patients applied their ointments twice daily from the first day until one month after radiation treatment was completed. The mean time to develop dermatitis was 3.7 weeks for the betamethasone group and 3.9 weeks for the Calendula group. No significant differences were observed in the incidence of symptoms such as burning, pruritus and pain between the two groups.

Key Finding: Calendula ointment demonstrated similar benefit to a moderately-potent steroid ointment in reducing acute radiation dermatitis.

Safety, Adverse Reactions, Herb-Drug Interactions

The effect of silymarin on oral nifedipine pharmacokinetics.

Fuhr U, Beckmann-Knopp S, Jetter A et al. *Planta Med* 2007; **73**(14): 1429-1435

Pharmacokinetic parameters were measured in 16 healthy male volunteers who received nifedipine (10 mg) either alone or with silymarin (280 mg administered 10 hours and 1.5 hours prior to the administration of nifedipine). Silymarin did not considerably change the extent of absorption or the metabolism of nifedipine (based on the results of the mean area under the curve and mean maximum plasma concentration). A mean delay of absorption was however, observed. The variation in the results between individuals was higher than expected – especially for the maximum plasma concentration, and it is possible that silymarin may have contributed to this effect. Further study with repeated administration is required.

Key Finding: Preliminary results suggest that silymarin taken as a 280-mg dose does not change the bioavailability of the antihypertensive drug nifedipine. It may delay the absorption of the drug.

The effect of kava consumption on liver function tests.

Kumar B, Kaur J. *Clin Chem* 2007; **53**(6, Suppl S): A50

A cross-sectional study in Fiji involving 101 participants investigated the potential adverse effects of traditionally prepared (water-extracted) kava (*Piper methysticum*). Kava consumers had been using kava for more than 3 months, non-kava consumers had either never consumed kava, discontinued use for a year or had consumed less than once in 3 months. Venous blood was collected and the results of liver function tests were compared between the two groups. Significantly and abnormally high serum GGT (gamma-glutamyl transferase) and ALP (alkaline phosphatase) were observed in kava consumers.* These enzymes showed a strong association with kava consumption and total lifetime consumption. However, there was no association between kava and clinically significant adverse health effects.

Key Finding: Moderate use of kava as a traditionally-prepared beverage in Fiji was not associated with adverse health effects.

Reviewer's Notes:

* The elevations probably represent an induction of these enzymes in response to kava, rather than liver damage (*Eur J Gastroenterol Hepatol* 2003; **15**(9): 1033-1036). This is supported by the results of a health status review of kava users in 1988: plasma levels of GGT were greatly increased in kava users, but no cases of acute liver injury were identified.

Water-extract kava preparations used at the recommended dosage are therefore unlikely to be associated with adverse health effects.

Disease Understanding, Diet, Lifestyle

Elevated plasma homocysteine and low vitamin B-6 status in nonsupplementing older women with rheumatoid arthritis.

Woolf K, Manore MM. *J Am Diet Assoc* 2008; **108**(3): 443-453

A small cross-sectional study involving older female participants found significantly elevated plasma total homocysteine levels in those with rheumatoid arthritis compared to healthy controls. Participants in this study were not using B-vitamin supplements. Serum pyridoxal 5'phosphate (PLP, the metabolically active coenzyme form of vitamin B6) levels were lower in the rheumatoid arthritis participants compared to controls, despite similar dietary intakes for vitamin B6. Total cholesterol and low-density lipoprotein cholesterol levels were significantly lower in the rheumatoid arthritis group. No significant differences were found for plasma folate, vitamin B12 or transcobalamin II (a carrier protein for vitamin B12) or for dietary intake of protein, fat and vitamin B12. Those with rheumatoid arthritis appear to have altered metabolism of vitamin B6. Poor vitamin B6 status and the resulting elevated plasma homocysteine levels may be one reason why those with rheumatoid arthritis have an increased risk of cardiovascular disease. (It is possible that hyperhomocysteinaemia rather than hyperlipidaemia is a primary contributor to the accelerated cardiovascular mortality associated with rheumatoid arthritis. Previous research focussed on the role of drugs used to treat rheumatoid arthritis and how they affected homocysteine metabolism: pencillamine lowered plasma homocysteine, whereas sulfasalazine and methotrexate increased it. Folic acid is prescribed along with methotrexate to prevent increases in plasma homocysteine levels.)

Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies.

Renehan AG, Tyson M, Egger M et al. *Lancet* 2008; **371**(9612): 569-578

Researchers in the United Kingdom conducted a meta-analysis of prospective studies to determine the risk of cancer associated with a 5 kg/m² increase in body mass index (BMI). (A 5 kg/m² increase in BMI corresponds to weight gains of about 15 kg in men and 13 kg in women who have an average BMI of 23 kg/m².) The meta-analysis reviewed studies from 1966 to November 2007, including 282137 cases from populations in North America, Europe, Australia and the Asia-Pacific region. They found this increase in BMI was strongly associated with oesophageal adenocarcinoma, thyroid, colon and renal cancers in men, and endometrial, gallbladder, oesophageal adenocarcinoma and renal cancers in women. Weaker positive associations were found between increased BMI and:

- rectal cancer and malignant melanoma in men
- postmenopausal breast, pancreatic, thyroid and colon cancers in women
- leukaemia, multiple myeloma and non-Hodgkin lymphoma in both sexes

The meta-analysis included the most rigorous studies, but some potential confounding variables could not be eliminated e.g. the use of hormone replacement therapy and mammographic density in the breast cancer studies and the effect of cigarette smoking in oesophageal adenocarcinoma.

Fructose intolerance in IBS and utility of fructose-restricted diet.

Choi YK, Kraft N, Zimmerman B et al. *J Clin Gastroenterol* 2008; **42**(3): 233-238

A study in the United States examined the prevalence of fructose intolerance in patients with suspected irritable bowel syndrome (IBS) and whether IBS patients can benefit from a fructose-restricted diet. If fructose is ingested in large quantities, the capacity of the gut to absorb fructose can be easily overwhelmed leading to fructose malabsorption.

Two hundred and nine patients with suspected IBS were retrospectively evaluated: 80 fulfilled the Rome II criteria for IBS and 31 of these demonstrated a positive breath test after fructose challenge (and hence fructose intolerance). The fructose intolerant patients received instructions for a fructose-restricted diet, for example how to avoid food items such

as fruit juice, cola products, carbonated beverages, corn products, chocolates and foods containing high fructose corn syrup. Their symptoms, compliance and the effects of dietary modification were assessed one year later. Of 26 patients, 14 were compliant with the diet and abdominal pain, belching, bloating, fullness, indigestion and diarrhoea had significantly improved. Noncompliance was associated with persistent symptoms.

Reviewer's Note: In a similar, earlier trial conducted in Australia (*J Am Diet Assoc* 2006; **106**(10): 1631-1639), 74% of patients responded positively in all abdominal symptoms when assessed after a period of dietary restriction (a median of 14 months). A positive response overall was significantly better in adherent patients compared to the nonadherent, as was improvement in individual symptoms. This paper gives extensive details about unfavourable foods – those containing excess free fructose (fructose greater than glucose) and more than 3 g per serving), and favourable foods including fruits where glucose is in balance with, or in excess of fructose is also provided.

Energy intake at breakfast and weight change: prospective study of 6,764 middle-aged men and women.

Purslow LR, Sandhu MS, Forouhi N et al. *Am J Epidemiol* 2008; **167**(2): 188-192

The association between energy intake consumed at breakfast and weight change was investigated in a prospective, population-based, cohort study involving middle-aged men and women in the United Kingdom. Recruitment started in March 1993 and was completed by the end of 1997, when a baseline health check was conducted. A follow-up health check was completed between 1998 and 2000. After excluding volunteers with incomplete food diary data, 6764 participants remained for analysis. The percentage of total energy intake (%TEI) consumed at breakfast ranged from 0% to 50%. Mean body mass index (BMI) at baseline was *lowest* (26.0) among persons in the highest group of %TEI at breakfast (22–50%), despite higher daily total energy intake (8506 kJ/day; see table below). All participants gained weight over the follow-up period, but the weight change was inversely associated with %TEI at breakfast. This means that those who consumed a greater proportion of their daily energy intake at breakfast gained relatively less weight. This association was independent of age, sex, smoking, total energy intake, plasma vitamin C level, social class, physical activity and intake of fat, carbohydrate, protein, fruit and vegetables. The association did not appear to be mediated by a corresponding reduction in %TEI consumed in the evening. Redistribution of daily energy intake, so that more energy from food and beverages is consumed at breakfast and less energy is consumed later in the day, may help to reduce weight gain in middle-aged adults.

	%TEI consumed at breakfast				
	0–11%	12–14%	15–17%	18–21%	22–50%
Baseline (1993–1997)					
body mass index (BMI, kg/m ²)	26.3	26.3	26.2	26.3	26.0
total energy intake (kJ/day)	8158	8125	8204	8314	8506
fruit and vegetable intake (g/day)	239	258	266	254	274
Follow-up (1998–2000)					
weight gain (kg)	1.23	1.17	1.19	1.02	0.79

Note: All results shown here were significant for the trend (p < 0.001).

Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley.

Roberts EM, English PB, Grether JK et al. *Environ Health Perspect* 2007; **115**(10): 1482-1489

Researchers in the United States investigated the association between *in utero* residential exposure to specific agricultural pesticides and the development of autism spectrum disorders (ASD) using a retrospective, case-control design. Four hundred and sixty-five children with ASD born during 1996–1998 were matched by the maternal date of the last menstrual period to 6975 live-born, normal-birth-weight, term infants as controls. Proximity to pesticide applications (in both time and space) was determined using California Department of Pesticide Regulation and the Department of Water Resources records. It was assumed that substantial population exposure due to pesticide drift was unlikely at distances greater than 1000 m and may be restricted to distances smaller than a few hundred metres. The periods immediately before and during central nervous system embryogenesis, neural tube closure and entire gestation

were notes as they could represent critical windows for exposure. The analysis compared children of mothers living within 500 m of field sites to those with mothers not living near field sites.

Risk for ASD was consistently associated with residential proximity to organochlorine pesticide applications occurring around the period of central nervous system embryogenesis (clinical weeks 1 through 8). This association appeared to increase with dose and reduced with increasing distance of residence from the field site. Further study is required to verify the association.

Reviewer’s Note:

Research presented at the 7th Annual International Meeting for Autism Research in May 2008 found:

- in a Californian case-control study that mothers of children with ASD were twice as likely to report that they had shampooed their pets with pyrethrin-containing antiflea/antitick shampoos around the time of their pregnancy (the association was strongest for the second trimester)
- in a study of low-income Mexican farmworker families in California that organophosphates were associated with ASD in children

Characteristics associated with older adolescents who have a television in their bedrooms.

Barr-Anderson DJ, van den Berg P, Neumark-Sztainer D et al. *Pediatrics* 2008; **121**(4): 718-724

A cross-sectional study in the United States investigated the characteristics of older adolescents (aged 15–18 years) who have a television (TV) in their bedroom. This study was a continuation of a project in which 4746 junior and senior high school students completed surveys and anthropometric measurements during the 1998–1999 school year. Participants were resurveyed by mail 5 years later. The current research examined adolescents who had not yet entered young adulthood. After loss to follow-up and incomplete information, data from 781 adolescents remained for analysis. They had a mean age of 17.2 years, with 60% in 12th grade, about 20% in 11th grade and about 20% not in school. Sixty-two percent of teenagers reported having a TV in their bedroom.

Adolescents with a bedroom TV differed according to gender, race/ethnicity and socioeconomic status and exhibited more unhealthy behavioural patterns than those without a bedroom TV. The results are outlined in the following table and were statistically significant. Twice as many adolescents with a TV in their bedroom were heavy TV users (watching more than 5 hours/day), compared with those without a TV in their bedroom.

Characteristics of those with a bedroom TV*	
Girls	Boys
more TV watching (20.7 vs 15.2 hours/week)	more TV watching (22.2 vs 18.2 hours/week)
lower vegetable intake (1.7 vs 2.0 servings/day)	lower fruit intake (1.7 vs 2.2 servings/day)
fewer family meals (2.9 vs 3.7 meals/week)	fewer family meals (2.9 vs 3.6 meals/week)
more sweetened beverage consumption (1.2 vs 1.0 servings/day)	lower grade point average (2.6 vs 2.9)
less vigorous physical activity (1.8 vs 2.5 hours/week)	

* compared to those without a TV in their bedroom

Note: Data gathered for TV viewing did not distinguish between total TV viewing and time spent watching TV in the bedroom only.