

Reviews of articles on medicinal herbs

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These abstracts are brief summaries of articles which have appeared in recent issues of herbal medicine journals, many of which are held in the NHAA library.

Silymarin neuroprotective effects

Hou Y, Liou K, Chern C, Wang Y, Liao J, Chang S, Chou Y, Shen Y. 2010 Preventive effect of silymarin in cerebral ischemia reperfusion-induced brain injury in rats possibly through impairing NF- κ B and STAT-1 activation. *Phytomed* 17:12;963-73.

Silymarin and silybin are some of the major bioactive constituents of St Marys Thistle (*Silybum marianum*), displaying potent anti-inflammatory and antioxidative activity. These effects may be useful in reducing neurological injury induced by ischemic stroke. The major pathological mechanism underlying ischemic/reperfusion injury to brain tissue is a phenomenon known as 'excitotoxicity' in which excessive release of glutamate (which builds up in the extracellular spaces after stroke onset) causes an inappropriate activation of ionotropic N-methyl-d-aspartate (NMDA) receptors in the brain. It basically excites neurons to death via excessive production of reactive oxygen species (ROS). A number of free radical producing enzyme systems are involved. ROS and reactive nitrogen species damage brain tissue via lipid peroxidation or protein nitrosylation of cell organelles and cell membrane, as well as by direct attacks on DNA.

In this research investigators set out to determine whether pre or post treatment with the flavonoids silymarin and silybin could protect mice from cerebral ischemic/reperfusion (CI/R) injury. Solutions containing silymarin or silybin, along with a sham solution, were given intravenously 15 min before (pretreat) or 60 min after (posttreat) RMCA occlusion at three different doses (1, 5 or 10 mcg/kg).

Silymarin but not silybin dose dependently (1-10 mcg/kg iv) reduced CI/R induced brain infarction by 16-40%. It also reduced pathophysiological biomarkers of brain injury (normally elevated in CI/R), including lipid peroxidation, protein nitrosylation and oxidative stress. Silymarin, but again not silybin, prevented expression of inflammation associated proteins and transcriptional factors, as well as proinflammatory cytokine production. This flavonoid may inhibit nitric oxide and superoxide anion production by interfering with NF- κ B nuclear translocation/activation.

This is the first piece of research to show that silymarin may reduce ischemic tissue damage to the brain in addition to its already proven ability to protect the kidney, myocardium and liver from these types of injury. Silymarin had more protective effects when

given prior to injury, potentially indicating that it may function via indirect modulation of early inflammatory signals rather than by direct interference with nitric oxide synthase. The promising results of the trial suggest that further investigation into the extract as a neuroprotective agent is warranted.

Anticandidal effects of holy basil

Amber K, Aijaz A, Immaculata X, Luqman K, Nikhat M. 2010. Anticandidal effect of *Ocimum sanctum* essential oil and its synergy with fluconazole and ketoconazole. *Phytomed* 17:12;921-5.

For a number of years conventional treatment and prevention of candidiasis often centres around the use of fluconazole, which has contributed to the growing drug resistance of *Candida albicans* and other fungal species. Thus there seems a need for alternative treatment options, particularly those which may be fungicidal not simply fungistatic.

Ocimum sanctum, otherwise known as holy basil, is used in Ayurvedic medicines for its antibacterial effects. Researchers in New Delhi recently set out to assess the antifungal activity of the essential oil of this plant and its synergy with fluconazole and ketoconazole. The oil was prepared by hydrodistillation and then analysed. It was found to be made up of 53 compounds, predominantly methychavicol (45%), linalool, carvone and D-limonene.

Essential oil of *O. sanctum* was found to be active against all 84 tested strains of *Candida*. The two highest ingredients, linalool and methychavicol were also the herbs most powerful when isolated. Holy basil essential oil displayed significant synergism with the two antifungal drugs tested. In addition the in vitro hemolytic assay (which is a model of host cell cytotoxicity) suggested that essential oil of *Ocimum sanctum* was significantly less toxic than the pharmaceutical products.

Passionflower activities vary by extraction method

Elsas S, Rossi D, Raber J, White G, Seely, C Gregory W, Mohr C, Pfankuch T, Soumyanath A. 2010. *Passiflora incarnata* L. (passionflower) extracts elicit GABA currents in hippocampal neurons in vitro and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method. *Phytomed* 17:12;940-9.

Passiflora incarnata (passionflower) is indigenous to America but is utilised worldwide making an appearance in the pharmacopeias of Switzerland, Germany, France, Great Britain, India, the USA and a number of other

countries. Its primary uses are in the treatment of anxiety, insomnia and epilepsy. To this date there has been a paucity of research clarifying the active constituents, although they are believed (on current evidence) to be the flavonoid components. Clinical trials have shown anxiolytic and sedative effects.

In preparation for a clinical trial in epilepsy sufferers, researchers in the United States conducted this research into the potential mechanisms of passionflower extracts and the impact of differing extraction methods on biological effects and extract components.

An initial whole plant extract was prepared by steeping the herb in 45% alcohol then freeze drying it to a powder containing 27.78 g fresh herb per 1 g of powder. When applied to a hippocampal slice preparation (mouse), this evoked a direct dose dependant increase in GABA_A currents. However a later amino acid reduced extract had no effects, leading researchers to suggest that it was the GABA_A in passionflower itself that induces changes in GABAergic transmission.

Following this experiment five further extracts were prepared from the same original source material. These were as follows:

1. Fresh herb steeped for 14 days in a 65:35 OH:H₂O mix at 25°C.
2. Fresh herb extracted in water at 100°C for 75 minutes then 4°C for 21 hours.
3. Dried herb steeped for 14 days in a 65:35 OH:H₂O mix at 4°C.
4. Dried herb extracted for 65 minutes in a 65:35 OH:H₂O mix at 100°C then 19 hours in the same mix at 4°C.
5. Dried herb extracted for 60 minutes in water at 100°C then 20 hours in the same mix at 4°C.

These were then tested in animal models of epilepsy, anxiety and sensorimotor function. Extracts 2 and 3 reduced the frequency and severity of seizures. Surprisingly all extracts increased measure of anxiety compared with control mice. Those which were the most anxiogenic were extracts 3 and 5. There was no effect on sensorimotor function displayed by any of the herbal preparations. It is suggested that differences between botanical species tested, geographical source of plants, extraction methods, dose, method and duration of administration, vehicle used, test animal species and strain, baseline anxiety levels and potential effects of the extracts on activity levels might all contribute to the divergence between these findings and those of other studies demonstrating the anxiolytic effects of passionflower. They also suggest that perhaps certain flavonoid constituents show different dose/response profiles with increased anxiogenic effects at higher doses.

Researchers examined the differing constituents present in these five extracts but found no correlation between total flavonoid or GABA content and displayed activities. Unfortunately this study fails to shed definitive light on the true active ingredients of *Passiflora*

incarnata, but suggests that further investigation (especially into potential synergism and biochemical activities) may be warranted.

French maritime pine bark for chronic venous insufficiency

Cesarone M, Belcaro G, Rohdewald P, Pellegrini L, Ledda A, Vinciguerra G et al. 2010. Improvement of signs and symptoms of chronic venous insufficiency and microangiopathy with Pycnogenol®. *Phytomed* 17:12;835-9.

Chronic venous insufficiency (CVI) is a common condition of decreased venous return resulting from dysfunctional valves. An extract of *Pinus pinaster* Ait (maritime pine) known as Pycnogenol® (which is standardised to contain 70±5% procyanidins) has been extensively used and researched for the treatments and prevention of this condition and its complications. It has been shown to control increased capillary permeability in the microangiopathy associated with CVI, prevent edema and is anti-inflammatory and antiplatelet, with beneficial flow on effects for venous pressure.

The current study utilised this extract in order to assess its efficacy in relieving the symptoms of CVI in volunteers with severe venous insufficiency and microangiopathy. Ninety eight volunteers with severe longstanding CVI were recruited and randomised into three groups which were comparable in age and gender make up. Upon inclusion, all were found to have significantly increased ambulatory venous pressure associated with incompetence of the deep venous system.

Two groups of patients received Pycnogenol® capsules (50 mg) thrice daily for eight weeks. One group used this in combination with compression stockings, and the other used only the herbal extract. The third and final group received no medication and used only compression stockings. These stockings were below knee height, with a pressure of 25 mmHg compression at the ankle and were worn for at least 10 hours daily during activity hours.

Researchers assessed microcirculatory measurements via strain gauge plethysmography (a test which quantifies capillary filtration at the ankle) and laser Doppler flowmeters. There was also a score for evaluation of clinical symptoms and signs including edema, pain, restless limbs, subjective swelling and skin redness or alterations. These symptoms were patient rated on a VAS and investigators assessed the severity with the aid of a venous clinical severity score. Disability was judged according to a 4-scale venous disability score.

Following eight weeks of treatment the combination group showed a significantly greater decrease in resting flux than the other two groups (who also displayed improvements in this measure). The Pycnogenol® alone was more effective than compression alone in this regard. There was also a significant increase in transcutaneous pO₂ respiration in both herbal groups, but a decrease in this measure with compression treatment alone. Capillary

filtration significantly decreased, symptomatic scores on the analogue scale significantly improved, clinical severity scores dropped and the venous disability score was improved in all three groups, with all parameters improved most by combination treatment, then Pycnogenol[®], then compression treatment alone.

Use of this standardised French maritime pine extract had beneficial effects on both signs and symptoms of CVI in those with severe venous insufficiency and microangiopathy. In comparison to compression treatment it was proven more effective, probably due to the ability to physiologically reduce increased capillary filtration rather than simply shift the physical site of edema. In conclusion the study proves the benefits of Pycnogenol[®] in the management and treatment of edema and other signs and symptoms of CVI.

Cinnamon and hormonal modulation

Iwaoka Y, Hashimoto R, Koizumi H, Yu J, Okabe T. 2010. Selective stimulation by cinnamaldehyde of progesterone secretion in human adrenal cells. *Life Sci* 86:23-24;894-8.

The bark of *Cinnamomum cassia* (and other species) has traditional indications in the female reproductive tract. While much research has investigated its digestive and blood sugar balancing effects, this herb also has strong traditional indications for dysmenorrhea and infertility. Cinnamaldehyde is a major constituent isolated from cinnamon bark and has demonstrated ability to stimulate catecholamine release from the adrenal glands in previous research.

This experiment was designed to investigate the effects of cinnamaldehyde on the secretion of steroid hormones, particularly progesterone, using the NCI-H295R cell line (which has been shown to express all the key enzymes of steroidogenesis, and thus has the ability to produce the steroid hormones normally found in the adult adrenal cortex).

Researchers exposed the cells to trans-cinamaldehyde at various concentrations for 24 hours. Steroid hormones in the cultured medium were measured by a highly sensitive LC-electrospray ionization tandem mass spectrometry.

Results demonstrated a dose dependent increase in progesterone concentrations in the cultured medium and a decrease in testosterone and dehydroepiandrosterone release. Cortisol and estradiol concentrations were also marginally lower, but this was not considered significant. The action of the herbal constituent is hypothesised to be due to suppression of 17 α -hydroxylase activities (one of the enzymes acting on pregnenolone to influence the relative amounts and nature of subsequent steroid products). Cinnamaldehyde was shown to increase cAMP release in the cultured medium and this may be responsible for the effects. However the mechanism of action was not a focus of this study and further investigations are required to elucidate the exact nature of the cinnamaldehyde effects.

Researchers suggest that the progesterone up-regulating activity of cinnamaldehyde may be of use in dysmenorrhea. This is due to the fact that progesterone may have an inhibitory action on Cox-2 expression in the endometrium and thus decrease the concentration of arachidonic acid metabolites in the area.

Anticancer effects of *Uncaria tomentosa*

Pilarski R, Filip B, Wietrzyk J, Kuraś, Gulewicz K. 2010. Anticancer activity of the *Uncaria tomentosa* (Willd.) DC preparations with different oxindole alkaloid composition. *Planta Med* 17:14;1133-9.

The natives of Peru have used *Uncaria tomentosa*, cat's claw, as a medicinal plant since ancient times. More recently the plant has become popular as an immunomodulatory, anticancer and anti-inflammatory remedy. It has also been used to treat gastric ulcers, diarrhea, gonorrhoea, arthritis, diseases of the urinary tract and cancers.

Chemical studies have revealed the presence of alkaloids, quinovic acid, glycosides, polyhydroxylated triterpenes, flavonoids and catechins in cat's claw, with some compounds showing a potentiation of phagocytosis by white blood cells. The aim of this study was to investigate the qualitative and quantitative differences in varying extraction methods. The bark of *U. tomentosa* was extracted by several different preparations: in water at 37°C (B/W₃₇), in boiling water (B/W_b), in 50% ethanol at 37°C (B/50E₃₇), in boiling 96% ethanol (B/E_b), in 96% ethanol at 37°C (B/96E₃₇) and in water and dichloromethane (B/SRT). IC₅₀ values were calculated for different oxindole alkaloid compositions.

Results showed a high correlation between the total oxindole alkaloid content and the antiproliferative activity of the preparations. B/96E₃₇ and B/SRT were the most cytotoxic, while lowest activity was found for the B/W₃₇. The B/96E₃₇ was active against Lewis lung carcinoma, cervical carcinoma and colon adenocarcinoma. B/SRT was particularly effective in inhibition proliferation of cervical carcinoma, breast carcinoma and lung carcinoma. Further animal studies did show significant inhibition of Lewis lung carcinoma growth by B/W₃₇ given for 21 days at daily doses of 5 and 0.5 mg.

Recommendations informally adopted in Western Europe suggest concentrations of oxindole alkaloids should be below 1.75% in medicinal preparations which would be found only in the B/W₃₇, B/25E₃₇ and possibly B/50E₃₇, while preparations containing over 50% of alkaloids such as B/E_b and B/96E₃₇ should not be used. However existing toxicological data does indicate that even pure oxindole alkaloids are safe to use.

The LD₅₀ value (determined in mice) suggests that lethal poisoning of an adult person weighing 70 kg would require consumption of 2 kg of the B/SRT preparation. All tested preparations were considered non toxic and well tolerated.

Zingiber and liver function

Heeba GH, Abd-Elghany MI. 2010. Effect of combined administration of ginger (*Zingiber officinale* Roscoe) and atorvastatin on the liver of rats. *Phytomed* 17:14;1076-81.

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are recognised as the most efficient drugs for the treatment of hyperlipidemia. Studies in animals suggest that statins may cause hepatotoxicity and accordingly statins require the monitoring of liver enzymes, particularly when given in high doses.

Atorvastatin (AT) has a longer action than other statins and presents active metabolites which are biotransformed mainly by cytochrome P3A4 in the liver. It has been suggested that AT may trigger autoimmune hepatitis, with cases of AT induced acute hepatitis, acute cholestatic hepatitis after AT treatment and a case of liver failure being reported.

Zingiber officinale, ginger, contains phenolic compounds that have antioxidant, anti cancer, anti-inflammatory and antithrombotic properties, and has been shown to significantly reduce plasma cholesterol levels. Studies have shown that long term feeding of ginger has hypoglycemic, hypolipidemic and anti-atherosclerotic effects in rats and cholesterol fed rabbits. Further animal studies have shown that ginger has hepatoprotective effects against ethanol, carbon tetrachloride and acetaminophen induced hepatotoxicity.

This study evaluated the possible protection of ginger extract (GE) against low and high doses of AT induced hepatic damage in rats. The animals were divided into groups given GE alone, AT alone, AT and GE, AT and vitamin E at varying doses.

Results showed significant reduction in total cholesterol levels in animals treated with either GE or AT compared with control groups. Concurrent administration of AT with GE or vitamin E also significantly decreased total cholesterol levels. The synergistic effect of combined administration of AT and GE on reduction of total cholesterol levels was found at lower doses of AT (20 mg/kg) while it was lost at higher dose of AT (80 mg/kg). No significant change in triglyceride levels was seen.

Results suggest combined treatment of ginger extract and low dose statins could be useful in treating hypercholesterolemic patients susceptible to liver function abnormalities.

Herbal medicine in pregnancy

Dugoua J-J. 2010. Herbal medicines and pregnancy. *J Popul Ther Clin Pharmacol* 17:3;e370-8.

This paper, presented at the Drugs in Pregnancy and Lactation Symposium in Toronto, Canada in June 2010, reported that the use of herbal medicines in pregnancy varies enormously dependent on the geographic area, sociocultural aspects and ethnicity, with figures ranging from 7% to 55% usage with up to 93% of midwives

prescribing or administering herbal or natural health products (NHPs).

In a study on pharmaceutical drug use by 295 pregnant women, 37% reported non compliance with their existing medication based on concern over drug use during pregnancy and the preference for NHPs over prescription medications. The author stressed the importance of understanding the potential dangers of NHPs for women of childbearing age, particularly when trying to conceive.

Evidence based usage for NHPs includes:

- ginger (*Zingiber officinale*) and vitamin B6 for nausea and vomiting of pregnancy;
- red raspberry (*Rubus idaeus*) for shortening the second stage of labour, lowering the rate of forceps delivery, reducing the likelihood of artificial rupture of membranes or need for caesarean section;
- castor oil to increase the likelihood of initiating successful labour within 24 hours;
- probiotics to assist in the prevention of atopic disease in infants

Evidence for harm from NHPs includes the use of blue cohosh (*Caulophyllum thalictroides*) for its reported cardiovascular side effects in both the pregnant woman and the neonate.

Other evidence presented included:

- echinacea (*Echinacea* spp) showed no statistically significant difference between the test group and control group in its effect on spontaneous abortion or risk of malformation during pregnancy;
- herbs containing berberine (such as *Hydrastis canadensis*, *Berberis vulgaris*, *Berberis aquifolium*) may displace bilirubin bound to albumin and aggravate newborn jaundice - this is based only on rat studies over one week;
- the safety of St John's wort (*Hypericum perforatum*) rests on the case of a woman who started taking St John's wort at 24 weeks gestation and developed thrombocytopenia - the author did not attribute this to St John's wort;
- further studies on St John's wort found rates of major malformations were similar between the test groups of pregnant women on St John's wort, pregnant women on antidepressant medications and healthy pregnant women with no teratogenic exposure during pregnancy.

For approximately 60% of NHPs, safety in pregnancy is unknown although women continue to initiate taking these products during pregnancy. To provide best care clinicians must screen their patients for use of complementary and alternative medicines and stay up to date on research regarding these agents.

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