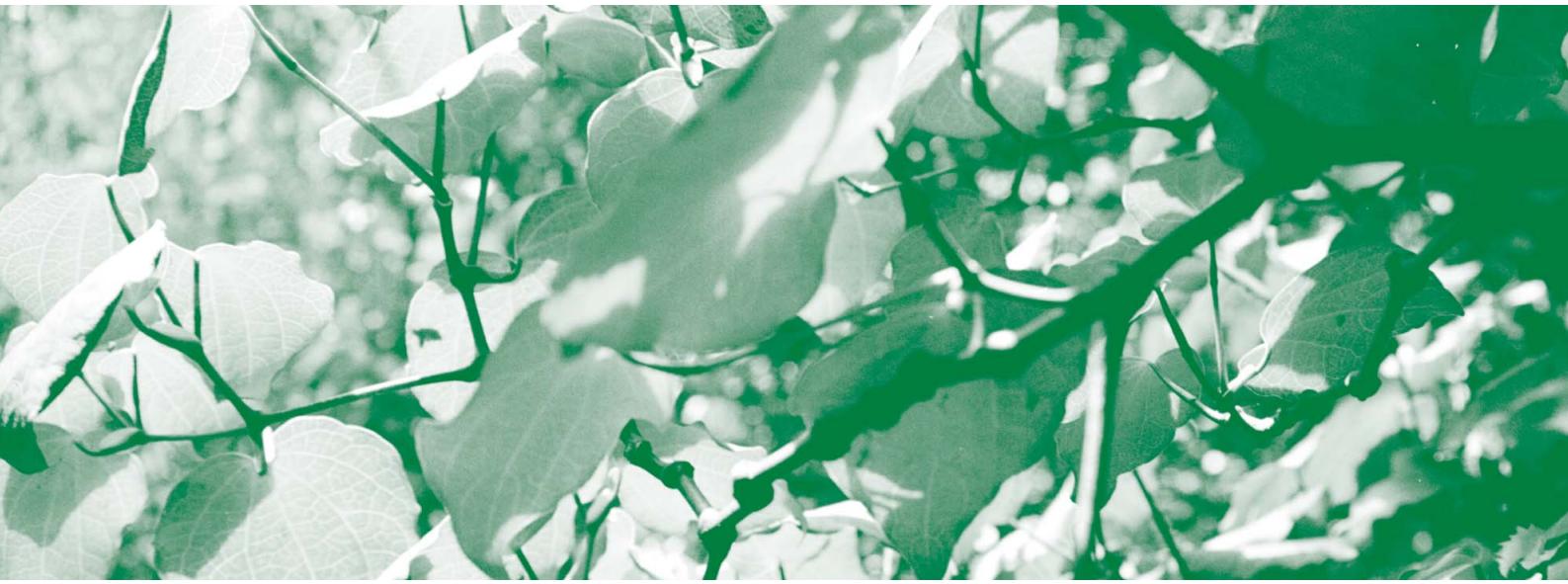
Phytonews

ISSN 1175-0251



St John's Wort more effective than paroxetine for severe depression

While numerous clinical trials have shown St John's wort (*Hypericum perforatum;* SJW) to be as effective as several other antidepressant drugs in the treatment of mild to moderate depression, its efficacy in patients with more severe depression is disputed. A team of researchers based in Berlin, in conjunction with the company which manufactures a well known brand of hypericum, have now reported favourable results for this phytomedicine in a study involving use of the antidepressant drug paroxetine (Aropax®) as a comparative treatment[1].

A total of 301 men and women aged 18 to 70 with single or recurrent moderate or severe episodes of unipolar major depression without psychotic features persisting for two weeks to a year, were recruited from 21 psychiatric care centres in Germany. All patients had a Hamilton depression scale score greater than 22 points, but patients with other psychiatric conditions or who had previously attempted suicide were excluded.

Continued page 2.

IN THIS ISSUE

PHYTOmed™ medicinal herbs ltd.
Manufacturers and suppliers of herbal extracts for practitioners

P.O. Box 83068.
Te Atatu South,
Auckland, New Zealand
Tel (09) 828 0040
Fax (09) 828 0039
Freephone 0508 PHYTOMED (749 866)

St John's Wort more effective than paroxetine for severe depression

Continued from the front page.

In the randomised, double blind and double dummy trial, patients were initially given either 300mg of a SJW extract three times daily plus one dose of paroxetine placebo daily, or one dose of 20mg/day paroxetine plus three doses of SJW placebo per day. These doses were doubled in patients whose total depression score had not decreased by at least 20% after two weeks of treatment. All participants underwent a preliminary screening examination to ensure adequate selection criteria. In each group more than half of the patients had a total depression score of 25 or more, thus meeting a diagnosis of severe depression.

The primary outcome measure was the absolute decrease of the Hamilton total depression score between baseline and week six. Secondary outcome measures included the Montgomery-Asberg depression rating scale, the clinical global impressions, and the Beck depression inventory. Assessment of adverse effects was also undertaken.

After two weeks of randomised treatment, 69 of the 122 patients in the SJW group (57%) and 58 out of 122 in the paroxetine group (48%) were switched to the higher doses.

At the end of the treatment period, 71% of patients in the SJW group and 60% of patients in the paroxetine group responded to treatment, with 50% of the SJW group and 35% of the paroxetine group showing remission. The increase in dose applied to non-responders after the first two weeks of treatment was shown to produce a marked increase in efficacy, for both antidepressants. Adverse effects (mainly gastrointestinal) were reported by 55% of patients in the SJW group, compared with 76% in the paroxetine group. No cases of photosensitivity reactions were associated with either the lower or higher dose of SJW.

Only one other study has been published to date involving SJW in the treatment of moderate to severe major depression, and this involved use of 1800mg/day of a SJW extract versus 150mg/day of the tricyclic imipramine, over a 6 week period[2]. While a comparable effect to imipramine was reported, the relatively small number of patients involved and other methodological quality parameters of this study, mean that it was not sufficiently powered to demonstrate non-inferiority of the SJW extract.

A recent meta-analysis of randomised controlled trials which paid particular attention to factors such as type and severity of depression and trial size, found little evidence of effectiveness in severe depression[3]. The fact that most of these involved a uniform standard dosage regimen however, as well as qualitative differences in the various SJW preparations used, could well have contributed to these relatively negative findings.

This German study provides convincing evidence that appropriate doses of a good quality SJW extract, is at least as effective as one of the most commonly used antidepressant drugs for the treatment of moderately or severely depressed patients. While this trial has some limitations in that it excluded patients with a high risk of suicide and was limited to a 6 week treatment period, it nevertheless shows that the frequently cited view that this phytomedicine is not effective in more seriously depressed patients, should be questioned.

Refs:
1. Szegedi A et al, *BMJ*, doi:10.1136/bmj.38356.655266.82, 11 Feb 2005.
2. Vorbach EU et al, *J Geriatric Psychiatry Neurol 7* (Supplement 1):S19 23, 1994.
3. Linde K et al, *Br J Psychiatry* 186:99-107, Feb 2005.

St John's Wort during pregnancy and lactation

Concerns regarding the use of St John's wort (*Hypericum perforatum*; SJW) during pregnancy and breastfeeding, have recently being raised following an Italian study involving treatment of female rats with a SJW extract both prenatally and during breastfeeding[1].

The study involved administering either SJW extract or water by gavage to 18 female rats, commencing two weeks before mating, throughout gestation, and for 21 days during breastfeeding. The livers, kidneys, lungs, hearts, brains and bowels of the offspring were then subject to microscopical examination. Two doses were used, 100mg/kg per day, and 1000mg/kg per day.

While no significant difference was observed in the number and weight of offsprings or maternal body weight during gestation, evidence of both liver and kidney damage was detected in the offspring of SJW-treated rats. This included focal hepatocyte damage and a reduction in glomerular size with disappearance of Bowman's space and hyaline tubular degeneration. In all cases, these lesions were much more evident in animals treated with the higher dose.

Little detail is given by the authors about their method of preparation of the SJW extract, although this was standardised for 0.3% total hypericin, and extracted in methanol, a known toxin to both the liver and kidneys. While methanolic rather than ethanolic extracts are frequently used in such animal studies, failure to document the method of preparation and dosage of actual methanol administered is a shortcoming, particularly when toxicity studies are concerned. The use of water only as a placebo in this study, rather than a comparable solution containing the same amount of methanol, would therefore seem to make its results somewhat questionable.

The lower dose of SJW extract administered in these tests (100mg/kg per day), was stated by the authors as being "comparable to the dose administered to humans, based on surface area". Consideration of the relative body weights of rats and humans however, leads to the conclusion that this dose would equate to approximately 12 grams of SJW per day in humans, some three to five times greater than that normally taken.

Other studies in animals have investigated the effects of SJW exposure during pregnancy on behavioural and cognitive development and physiological parameters in rats and mice[2,3]. These found no significant effects on cognitive tasks or neurobehavioural changes following prenatal exposure. Evidence of slight *in vitro* uterotonic activity has also been reported in guinea pigs and rabbits[4].

Unfortunately however, few human case reports involving SJW use during pregnancy or lactation have been published in the peer-reviewed literature to date. Two such reports which considered sporadic cases of SJW use during pregnancy did not find any significant side effect in mothers or infants[5,6]. A single case report of a 38 year old woman who developed late onset thrombocytopenia while taking SJW[5] has been published, but from an evidence-based perspective, a causative link remains highly speculative. While an observational study involving the effects on lactation of maternal SJW use reported a few cases of colic or drowsiness in breastfed infants, the statistical relevance of this was low[7,8].

The safety of conventional antidepressant drugs in this context, should also be considered. Recent studies on the safety of newer antidepressants in pregnancy and breastfeeding, found evidence of an association between placental exposure to selective serotonin reuptake inhibitors (SSRI's), and adverse but self-limiting effects on neonatal adaptation[9]. Alterations in biobehavioural responses, suggesting possible sustained neurobehavioural outcomes beyond the newborn period, have also been reported following prenatal and postnatal SSRI exposure[10]. Many uncertainties remain regarding the safety of SSRI use during pregnancy[11]. Information on teratogenic risks for a number of antidepressant drugs, is also either incomplete or lacking[9].

Recommendations concerning the use of medications during pregnancy, should involve a risk versus benefit analysis in each case. In certain situations, even where a potential risk to the foetus is thought to exist through drug use during pregnancy, the balance of clinical judgement leads to the decision to commence or continue with such prescribing with the well being of the mother and/or baby in mind.

In view of the lack of toxicity data, it is generally recommended that SJW should be avoided during pregnancy and lactation. Based upon the virtual absence of evidence of harm from its use during pregnancy in humans however, as well as the large amount of anecdotal information from unpublished case reports of pregnant women taking it, it is the author's opinion that this phytomedicine is still appropriate to use in certain cases, particularly where a high risk of post-natal depression exists. Nevertheless, as with various other antidepressant drugs, further properly designed studies in order to further investigate this subject, seem necessary.

Refs:
1. Gregoretti B et al. *Toxicol Appl Pharmacol*, 200(3): 201-205, Nov 2004.
2. Cada AM et al, *Nutr Neurosci* 4(2):135-141, 2001.
3. Rayburn WF et al, *Neurotoxicol Teratol* 23(6):629-637, 2001.
4. Shiplochliev T. *Vet Med Nauki.* 18(4):94-8 1981
5. Grush LR et al, JAMA 280(18):1566, 1998.
6. Klier CM et al. *Pharmacopsychiatry.* 35(1):29-30; Jan 2002
7. Lee A et al. *J Clin Psychiatry.* 64(8):966-8, Aug 2003
8. Rasmussen PL, *Phytonews* 18, ISSN 1175-0251, Phytomed Medicinal Herbs Ltd, Auckland, New Zealand, 2004.
9. Gentile S *Drug Safety* 28(2):137-152, 2005.
10. Oberlander TF et al. *Pediatrics.* 115(2):411-25. Feb 2005
11. Wen SW, Walker M. *J Obstet Gynaecol Can* 26(9):819-822, 2004.

Human metabolic responses to Chamomile

Chamomile has a lengthy tradition of use as a treatment for a wide range of digestive and menstrual conditions, and as a mild sedative and calming beverage. Despite its impressive reputation however, very few studies involving preparations made using whole chamomile flowers have been undertaken. Most published research to date relates to assessment of individual components or fractions, and studies on animals rather than humans.

English researchers have recently undertaken a study to determine the human biological responses to chamomile tea ingestion over a period of two weeks, preceded and followed by two week periods when no tea was taken but monitoring occurred[1]. A metabonomic strategy, using nuclear magnetic resonance (NMR) spectroscopy and complex statistical analyses, was used to detect a wide range of metabolites found in tissues and bodily fluids, including urine and blood plasma. Such NMR profiles of biofluids are a relatively new technique which can provide a large amount of information on the effects of a wide range of variables such as diet or therapeutic intervention, on the body's metabolic responses.

Fourteen male and female volunteers took a tea containing 5g of chamomile powder which was infused in 200ml of boiling water for 10 minutes then strained, and drunk once daily. This dose corresponds to a daily intake of approximately 5 cups of chamomile tea from commercial preparations. During the 2 week dosing period, this preparation was taken daily at the same time, and urine samples collected between 1.5 and 2 hours later. Dietary information from the preceding evening and morning prior to sample collection was recorded to identify any potential confounding dietary influences on the spectroscopy tests done on all urine samples. While a wide variation between the individual metabolite profiles for different subjects was observed, a model which filtered out possible confounding factors was validated and applied. Subsequent analysis of the biological responses to chamomile intake was then undertaken.

A clear differentiation between the samples obtained before and after chamomile ingestion was measured. The main effects seen were an increase in urinary excretion of hippurate, glycine, and an unknown metabolite, as well as decreased urinary excretion of creatinine.

Hippurate is a metabolite of many phenolic plant compounds including flavonols, and has been shown to exhibit antibacterial and antioxidant activity. Its excretion in urine has also been shown to correlate with the microfloral composition of the colon[2,3]. Glycine is an amino acid thought to act as a muscle and nervous system relaxant[4]. The fact that urinary levels of these compounds remained elevated for up to two weeks after the test subjects stopped drinking the tea, indicates that they may remain active in the body over a prolonged period. Disruption of the gut microbiotical colony due to the antimicrobial activity of chamomile, was suggested by the authors as accounting for this prolonged effect.

The researchers related the reduced urinary excretion of creatinine to the antioxidant effects of chamomile, as oxidative stress is known to promote urinary excretion of this compound[5,6].

This study provides valuable information on both the metabolism of chamomile following its ingestion in humans, but also implicates potential mechanisms of several of its reputed health benefits.

Refs:
1. Wang Y et al, *J Agric Food Chem* 53(2):191-196, 2005.
2. Nicholls AW et al, *Chem Res Toxicol* 16, 1395-1404, 2003.
3. Williams RE et al, *Xenobiotica* 32, 783-794, 2002.
4. Lynch JW. *Physiol Rev.* 2004 Oct;84(4):1051-95.
5. Almar M et al, *Free Radic Res* 36(3):247-253, 2002.
6. Ojkamura K et al *Free Radic Res* 26(6):507-514, 1997.

Pharmacokinetics of glycyrrhizin from liquorice

The use of isolated pure herbal compounds as opposed to whole plant extracts has become more common in recent years, yet clinical pharmacokinetic studies to compare the relative bioavailability of key compounds when administered by these two methods are often lacking.

Glycyrrhizin is a main and active (saponin) constituent of the root of Liquorice (*Glycyrrhiza spp*), used widely in both western phytotherapy and traditional Chinese medicine. A large number of pharmacological effects have been documented for glycyrrhizin, including anti-inflammatory, antacid, antioxidant and antiviral activities. Glycyrrhizin is hydrolysed to its active aglycone glycyrrhetinic acid by the bowel flora, a substance also found as a minor component of liquorice root.

Findings from a recent Taiwanese study which compared the pharmacokinetics of pure glycyrrhizin with that of glycyrrhizin obtained from a liquorice root decoction in rabbits, have added to our knowledge of the clinical pharmacokinetics of this important phytomedicine.

A randomised crossover design was used in the study, with rabbits being given pure glycyrrhizin or a liquorice decoction orally as aqueous solutions at equal dose of 300mg/kg of glycyrrhizin. Serum levels of glycyrrhizin and glycyrrhetinic acid were measured at various time points following administration, and pharmacokinetic curves prepared from the results.

The AUC's (areas under the curves measuring plasma concentration versus time) for both glycyrrhizin and glycyrrhetinic acid after dosing with pure glycyrrhizin were significantly lower than those after dosing with liquorice decoction by 70% and 34% respectively.

This study thus shows that in rabbits at least, the absorption of glycyrrhizin and glycyrrhetinic acid is substantially greater when given in the form of a liquorice decoction rather than as isolated glycyrrhizin.

Refs:
Hou Yu-Chi et al, *Life Sciences* 76, 1167-1176, 2005.

Black Cohosh and breast cancer

Speculation as to the safety of Black Cohosh supplements in the treatment of menopausal symptoms has occurred following release of results of a study in July 2003 which suggested Black Cohosh increased the risk of breast cancer metastasis[1]. While the logic of extrapolation of the results of this study, carried out on mice, to a human situation is limited, it did raise some concerns regarding the safety of women with active breast cancer taking supplements containing Black Cohosh.

More recently however, a study using various assays to assess the oestrogenic activity of black cohosh and examine its safety for those with or at high risk of developing breast cancer, failed to find evidence of oestrogenic activity or possible potentiation of metastases for black cohosh extracts[2]. Researchers in Switzerland have also recently demonstrated the ability of Black Cohosh extracts to inhibit the proliferation of both oestrogen receptor-positive and negative breast carcinoma cell lines through induction of cell death (apoptosis)[3,4]. These effects were shown to withstand simulated liver metabolism, and thus probably occur also following oral administration.

These results are in line with other *in vitro* studies conducted on human breast cancer cell lines which have found that black cohosh at clinically significant concentrations can both inhibit breast cancer cell proliferation[5,6] and potentiate anti-cancer effects of the oestrogen antagonist drug tamoxifen[7]. Protective effects against DNA damage have also been reported for this phytomedicine[8], and animal studies have revealed evidence of inhibitory effects against development of both prostate[9] and endometrial cancer[10].

Two clinical trials to date have evaluated combined administration of black cohosh with tamoxifen or black cohosh alone in women who had survived breast cancer[11,12]. Black cohosh was shown to be safe in both trials, and in one of these where combined tamoxifen and black cohosh treatment occurred over a 12 month period, the frequency of severe hot flushes (a frequent side effect of tamoxifen treatment) was reduced from 73.9% in the group receiving tamoxifen alone, to only 24.4% of women receiving both tamoxifen and black cohosh.

A review on the safety of black cohosh for the treatment of menopause symptoms, which evaluated all published literature pertaining to preclinical and clinical safety, and the FDA and WHO adverse-event reporting systems, was published in 2003. This concluded that specific black cohosh extracts are a safe alternative for women in whom oestrogen therapy is contraindicated[13]. A low incidence of adverse events (5.4%) was reported and of these 97% were minor and did not result in discontinuation of treatment.

These recent studies would seem to provide further reassurance of the safety of black cohosh when taken by women with a history of breast cancer, although further larger and more long term studies are still required.

Refs:

1. Unpublished paper presented by Dr V. Davis at the American Association for Cancer Research Annual Meeting, 11-13 July 2003.
2. Lupu R et al, *Int J Oncol* 23(5):1407-1412, Nov 2003.
3. Hostanska K et al. *Biol Phamr Bull.*27(12):1970-5; Dec 2004.
4. Hostanska K et al. *Breast Cancer Treat.* 84(2):151-60; Mar 2004.
5. Dixon-Shanies D, Shaikh N. *Oncol Rep.*;6(6):1383-7. 1999 Nov-Dec
6. Einbond LS et al, *Breast Cancer Res Treat* 83(3):221-231, 2004.
7. Burdette JE et al. *J Agric Food Chem.* 20;50(24):7022-8. 2002 Nov
8. Amato P, Christophe S, Mellon PL. *Menopause*; 9(2):145-50. 2002 Mar-Apr.
9. Ng SS, Figg WD. *Anticancer Res* 23(5A):3585-90, 2003.
10. Nisslein T, Freudenstein J. *Toxicol Lett* 150(3):271-275, May 2, 2004
11. Hernandez Munoz G, Pluchino S. *Maturitas* 44 Suppl 1:S59-65, Mar 14, 2003.
12. Jacobson JS et al, *J Clin Oncol* 19(10):2739-45, 2001.
13. Dog TL et al. *Menopause* 10(4):299-313, Jul-Aug 2003.

Ginkgo and PAF inhibition

Extracts of Ginkgo biloba leaf have been used for more than 20 years now to help improve cognitive function and for their protective effects against dementia and stroke, as well as for a range of other perceived benefits. A number of different mechanisms of action are thought to contribute to the effects of this plant on the cardiovascular system, including antioxidant, anti-platelet activating factor (PAF), and neuroprotective activities.

Numerous clinical trials and postmarketing surveillance data show a very good safety profile for ginkgo extracts, although several case reports of haemorrhage have been documented during ginkgo use[1,2,3,4,5,6,7]. In most of these cases however, patients were receiving concurrent anticoagulant drugs or other medications, and a clear causality between ginkgo intake and bleeding has yet to be established.

Platelet activating factor (PAF) is a potent platelet aggregating agent formed by platelets and various white blood cells, and the PAF inhibitory effects of ginkgolides found in ginkgo are usually cited as being responsible for an increased risk of bleeding, particularly when this is taken with anticoagulant or antiplatelet drugs. Inhibition of PAF can also induce bronchoconstriction and anaphylaxis, and PAF inhibition has been postulated to account for potential benefits of this phytomedicine in the treatment of atopic asthma[8,9].

The original determination of the activity of ginkgo as a PAF inhibitor however, involved experiments using rabbit platelets, and evaluation of possible PAF inhibition in a clinical setting or using human platelets, has remained uninvestigated until recently. Findings by a team of German researchers from a study involving PAF mediated induction of human platelet aggregation, have now provided some interesting results[10].

Aggregation of human platelets by PAF was measured *in vitro*, and the inhibitory effects of various ginkgolides found in ginkgo extract determined. Half maximal inhibition of PAF was found for ginkgolides B, A, C and J, at concentrations of 2.5, 15.8, 29.8 and 43.5 micrograms per ml, respectively.

The authors then compared these concentrations with published human pharmacokinetic data on ginkgo, and calculated that these concentrations required for PAF inhibition are generally more than 100 times higher than the peak plasma values measured after oral intake of a standardised ginkgo preparation at the normal recommended dose of 120 to 240mg day. Based upon these results, as well as the fact that PAF itself is considered a weak rather than strong platelet activator, they concluded that it is unlikely that any PAF antagonistic effect of ginkgolides could be responsible for haemorrhage in patients taking ginkgo preparations.

This study serves as a useful reminder that relating a pharmacological activity of one group of phytochemicals to an action produced by a phytomedicine containing them, needs to consider pharmacokinetic factors. It also challenges the alleged ability of ginkgo extracts to increase the risk of bleeding, when taken in normal therapeutic doses. Two randomised, placebo-controlled, double-blind studies in healthy volunteers conducted during the past 2 years, have failed to find evidence of any influence on platelet activity or coagulation, when ginkgo was taken for 7 to 14 days[11,12].

Refs:
1. Vale S. *Lancet* 352 (9121):36, 1998.
2. Rowin J & Lewis SL. *Neurology* 46(6): 1775-1776, 1996.
3. Gilbert GJ. Biloba. *Neurology* 48(4): 1137, 1997.
4. Miller LG, Freeman B, *J Herb Pharmacother* 2(2):57-63, 2002.
5. Hauser D et al, *Transpl Int* 15(7):377-9, 2002.
6. Meisel C et al, Atherosclerosis 167(2):367, 2003.
7. Fong KC, Kinnear PE. *Postgrad Med J* 79(935):531-2, 2003.
8. Roberts NM et al, *Br J Clin Pharmacol* Jul;26(1):65-72, 1988.
9. Braquet P, Hosford D, *J Ethnopharmacol.* Apr;32(1-3):135-9, 1991.
10. Koch E et al, Phytomedicine 12(1-2):10-16, Jan 2005.
11. Bal Dit Sollier C et al, Clin Lab Haematol 25(4):251-3, 2003.
12. Kohler S et al, *Blood Coagul Fibrinolysis.* 15(4):303-309, 2004.

New Ginkgo compounds implicated as anti-amnestic constituents:

Prolyl endopeptidase (PEP), is an enzyme which has been shown to play a role in the degradation of various proline-containing neuropeptides involved in the processes of learning and memory, such as vasopressin, substance P, and thyrotropin-releasing hormone[1]. Several compounds which inhibit PEP have been shown to result in a significant improvement in memory performance in animal studies, and the memory and performance improving ability of these is being evaluated as potential new nootropic drugs. Favourable activity of one such compound has now been shown in preclinical and clinical studies on both young and elderly healthy volunteers[2,3], and several PEP inhibitory compounds have been isolated from medicinal plants in recent years[4,5].

Significant activity of ginkgo leaf as a PEP inhibitor has recently been documented by Korean workers. Fractionation and column chromatography of the ginkgo extracts identified salicylic acid derivatives (6-(8'Z-pentadecenyl) salicylic acid, and 6-(10'Z-heptadecenyl) salicylic acid, as non-competitive inhibitors of this enzyme[6].

This finding implicates the possible contribution of other types of phytochemicals in addition to flavone glycosides and terpenoids, to the memory improving properties of ginkgo extracts.

Refs:
1. Atack JR et al, *Eur J Pharmacol* 205(2):157-163, 1991.
2. Morain P et al, *Br J Clin Pharmacol* 50(4):350-359, 2000.
3. Morain P et al, *CNS Drug Rev* 8(1):31-52, 2002.
4. Fan W et al, *Chem Pharm Bull* 48(7):1055-1061, 2000.
5. Kobayashi W et al, *Biol Pharm Bull* 25(8):1049-52, 2002.
6. Lee JH et al, *Planta Med* 70(12):1228-1230, 2004.

Person to person transmission of Avian Influenza

The emergence of new infectious diseases such as human immunodeficiency virus/acquired immune deficiency syndrome, avian influenza and SARS (Sudden Acute Respiratory Syndrome), has been of great concern to public health officials over the past few years.

Interspecies transmission of bacteria or viruses, appears to be increasing in frequency. Both SARS and avian influenza (influenza A, H5N1) arose in Asia and originated from animal viruses, yet both have the potential to mutate and adapt to enable human to human transmission through exchanging genetic material with a human influenza virus in a host simultaneously infected with both strains. Should this occur, a strain with pandemic potential could emerge in the human population, due to the fact that humans lack antibodies to the animal-derived antigens present on the viral surface.

Specific factors precipitating such emerging infectious diseases are also becoming increasingly prevalent (see *Phytonews 19*[1] for a discussion of these). These include ecological, environmental or demographic factors that place people in increased contact with the natural non-human host for a previously unfamiliar infectious agent, or that promote its spread. Highly concentrated poultry and pig farming, in conjunction with traditional live animal markets and the relative ease and availability of high speed and far-reaching transportation methods, provide optimal conditions for increased mutation, reassortment and recombination of influenza viruses.

Since the emergence of avian influenza in Hong Kong in 1997, the virus has gone through many reassortment events, resulting in the appearance of several new diverse genotypes[2,3,4]. The ability of some of these to become transmitted among animals including cats, ferrets, tigers and leopards has also now been shown[5,6,7].

Outbreaks of H5N1 avian influenza viruses in eight Asian countries during 2004, were highly lethal to poultry and infected at least 44 humans, killing 32 of these. A further outbreak is currently afflicting the Asian region, particularly Thailand and Vietnam where tens of millions of ducks, geese and other waterfowl are raised in backyard farms, and major culls are now underway[8].

Most people killed during last year's epidemic had been in close contact with poultry, and published evidence of efficient human to human transmission of avian influenza has remained lacking to date. A recent report from Thailand however, provides startling evidence that such viruses could well now be developing the ability to transmit directly from human to human[9].

An 11 year old girl who lived with her aunt, was admitted to hospital in early September 2004 with fever, moderate dyspnoea, lymphopenia and thrombocytopenia. A diagnosis of viral pneumonitis or the dengue shock syndrome was made, although a serum sample was negative for dengue virus antibodies. Despite intensive treatment including broad spectrum antibiotics, the patient died soon after admission to hospital.

Three days later, the girl's 26 year old mother, who lived in another province but had provided bedside care for her daughter in the hospital for 16 to 18 hours, developed fever and headache. She was admitted to hospital one week later with fever and severe dyspnoea, lymphopenia and thrombocytopenia, and died three days later.

The girl's aunt, a 32 year old woman who lived with her niece and provided bedside care for her for 12 or 13 hours the day before she died, developed similar symptoms 9 days after the girl's death, and was admitted to hospital a week later. An investigating team suspecting avian influenza, obtained respiratory specimens for testing, initiated treatment with the antiviral drug oseltamivir, and instituted full isolation precautions. The patient gradually improved, and she was discharged two weeks after admission.

While specimens were not obtained from the 11 year old girl and her body was cremated, autopsy tissue from the mother and nasopharyngeal and throat swabs from the aunt were positive for avian influenza A (H5N1). Clinical features as well as exposure to sick and dying poultry however, support a diagnosis of avian influenza in this girl.

Extensive epidemiologic findings revealed that the girl and her aunt had been in contact with free-ranging household chickens that had died soon prior to the girl's illness. The aunt did not however develop symptoms until 17 days after her last known exposure to poultry, beyond the accepted 2 to 10 days incubation period of avian influenza[10]. It was therefore deemed unlikely by the authors (who include staff from the U.S. Centers for Disease Control and Prevention) that she had contracted her illness from these birds. The mother also, who worked in a Bangkok garment factory, had experienced no known exposure to live or dead poultry in the two weeks preceding her illness, but had hugged and kissed her daughter when in hospital. The authors concluded that the most likely explanation for the family clustering of these three cases of avian

influenza, was direct transmission of the virus from the infected girl to her mother and to her aunt.

This is the first and most detailed report of probable person-to-person transmission of avian influenza, although the author's opinion is that direct transmission has probably occurred before. This is supported by the development of mild symptoms in one of the Hong Kong health care workers, and a Dutch report of three probably secondary infections among family members of poultry workers[11].

Children are often the major point of entry for the influenza virus into the household, and childhood infections with avian influenza viruses can be both severe as well as harbingers of the evolution of a pandemic strain. The increasing number of cases of avian influenza reported in Vietnamese and Thai children over recent months[12,13], is therefore of concern.

Of further concern is the fact that several recent cases involve an atypical presentation where respiratory symptoms were absent, indicating the broad clinical spectrum of avian influenza and the difficulty in diagnosis in some cases[12]. The presence of viable HSN1 virus in the faeces of one child, has also been reported[12].

These recent case reports have important implications for transmission, infection control and public health, and should serve as a stark reminder of the urgent need to prepare for a future influenza pandemic, which has the potential to be enormously lethal in the modern world. The 1918 influenza pandemic, also thought to have originated from an animal influenza virus, killed more people in a single year than the epidemic of bubonic plaque in the Middle Ages killed in a century[14]. A projection of an influenza pandemic in the U.S. made by the Centers for Disease Control and Prevention in 1999, estimated a total of 89,000 to 207,000 deaths, 314,000 to 734,000 hospitalisations, and 18 to 42 million outpatient visits, at a cost to society of at least US$71.3 billion[15]. A report commissioned by the New Zealand Ministry of Health and just published in the New Zealand Medical Journal, predicts a similarly frightening local impact of an outbreak of avian influenza. Such a pandemic could see more than more than a million New Zealanders needing to visit their doctor, put 20,000 more people in hospital, and result in 3,700 deaths[16]. Up to 1530 deaths and 8250 hospitalisations in Pacific Island nations were likely according to an earlier report by New Zealand researchers[17], who warned that a flu epidemic was likely if not inevitable.

With the increasing prevalence of these and other specific factors precipitating the emergence of infectious diseases such as antibiotic and antibacterial agent overusage[1], the burning issue now seems to be how soon the next pandemic will emerge. One can only hope that public health officials and politicians are taking these growing signs of a major outbreak seriously.

Refs:
1. Rasmussen PL. *Phytonews* 19. ISSN 1175-0251, September 2004.
2. Choi YK et al, *Virology* 332(2):529-537, Feb 20, 2005.
3. Li KS et al, *Nature* 430:209-213, 2004.
4. Suzuki Y. *Biol Pharm Bull* 28(3):399-408, 2005.
5. Kuiken T et al, *Science* 306:241, 2004.
6. Keawcharoen J et al, *Emerg Infect Dis* 10(12):2189-2191, 2004.
7. Govorkova EA et al, *J Virol* 79(4):2191-8, Feb 2005.
8. World Health Organization. *Wkly Epidemiol Rec* 80(5):41-42, Feb 4, 2005.
9. Ungchusak K et al, *N Engl J Med* 352(4):333-340, Jan 27, 2005.
10. Hien TT et al, *N Engl J Med* 350:1179-1188, 2004.
11. Fouchier RA et al, *Proc Natl Acad Sci USA* 101(16):6212-6216, 2004.
12. De Jong MD et al, *N Engl J Med* 352(7):686-691, Feb 17, 2005.
13. Chokephaibulkit K et al, *Pediatr Infect Dis* 24(2):162-166, 2005.
14. Taubenberger JK et al, *Philos Trans R Soc Lond B Biol Sci* 356:1829-1839, 2001.
15. U.S. Centers for Disease Control and Prevention, Atlanta, 1999
16. Jennings L, *NZ Med J* 118(1211), Mar 11, 2005.
17. Wilson N et al, University of Otago, Dunedin. *New Zealand Herald*, 24 Feb, 2005.

Avocados protective against prostate cancer?

The health promoting properties of avocado have become increasingly considered in recent years, due largely to its rich content of monounsaturated fatty acids. Recently, the content of other potentially beneficial substances found in this fruit, has been investigated. Based upon their yellow-green colour, Californian researchers measured the carotenoid content of Hass avocados (*Persea Americana*), and made some interesting findings[1].

Avocados were found to be the richest source of lutein among 20 commonly eaten fruits, and to contain significant quantities of vitamin E. Measurable amounts of related carotenoids such as zeaxanthin, alpha-carotene, and beta-carotene, were also detected.

Lutein has become best known for its beneficial effects as a protective against eye diseases such as cataracts and macular degeneration[2,3], and many lutein supplements are now available. Several studies have also implicated dietary intake of this and other carotenoids such as lycopene and beta-carotene, as having protective effects against the development of prostate cancer[4,5,6].

Based upon these earlier findings and the cytotoxic activity against six human tumour cell lines previously found for 3 different compounds found in avocado[7], the Californian researchers tested an acetone extract of avocado containing these carotenoids and tocopherols, with both androgen-dependent (LNCaP) and androgen-independent (PC-3) human prostate cancer cell lines *in vitro*. Inhibitory effects on the growth of both cancer cell lines was seen, and incubation of the PC-3 cells with avocado extract led to G(2)/M cell cycle arrest accompanied by an increase in p27 protein expression.

Lutein alone, did not produce these same inhibitory effects of avocado on cancer cell proliferation.

Other potential benefits of using avocado as a source of both lutein and other beneficial carotenoids have been documented by a team of nutritionists at the Department of Food Science and Technology and Internal Medicine at Ohio State University[8]. The addition of avocado to salsa was found to result in a marked increase in the absorption of lycopene and beta-carotene, resulting in 4.4 to 2.6 times the level of bioavailability (mean AUC, or area under the plasma concentration versus time curve), in healthy human volunteers. When 150g of avocado or 24g of avocado oil was added to a salad, absorption of alpha-carotene, beta-carotene and lutein was also increased dramatically, increasing the AUC by 7.2, 15.3 and 5.1 times respectively. The favourable effects of avocado in both this and the above study were primarily related to the lipid content of avocados.

Thus incorporation of avocado or avocado oil with vegetables such as tomatoes, salad and onions, has been shown to have major impact on absorption of their beneficial antioxidant nutrients. A synergistic effect on carotenoid absorption, and superior *in vitro* anti-cancer activity to that produced by lutein alone, would seem to relate to the presence of lipids and other phytochemicals in this increasingly popular food.

Refs:
1. Lu QY et al, *J Nutr Biochem* 16(1):23-30, Jan 2005.
2. Bartlett H, Eperjesi F. *Opthalmic Physiol* Opt 23(5):383-399, 2003.
3. Granado F et al, *Br J Nutr 90*(3):487-502, 2003.
4. Lu QY et al, *Cancer Epidemiol Biomarkers Prev* 10(7):749-756, 2001.
5. Binns CW et al, *Asia Pac J Clin Nutr* 13(Suppl):S117, 2004.
6. Jians L et al, *Int J Cancer* 113(6):1010-4, Mar 1, 2005.
7. Oberlies NH et al, *J Nat Prod* 61(6):781-785, 1998.
8. Unlu NZ et al, *J Nutr* 135(3):431-6, 2005.

Weekly baked fish cuts stroke risk in elderly

The preventative effects of regular fish intake on cardiovascular disease have been increasingly revealed from long term epidemiological studies in recent years[1]. These benefits appear to derive at least in part from the favourable oil profile and high content of omega-3 and omega-6 fatty acids of most fish relative to fats obtained from other animal sources.

Researchers from the Harvard School of Public Health, have now found that while baking or boiling fish is associated with a reduced risk of stroke in the elderly[2], fried fish can actually raise this risk.

The diets of 4,775 adults were monitored over a 12 year period, and the association between different types of fish meals and the risk of stroke in adults aged 65 years or over, evaluated. Those subjects who ate broiled or baked fish one to four times per week had a 28% lower risk of ischaemic stroke, while five or more servings per week produced a 32% lower risk. Those who ate regular fried fish or fish burgers however, experienced a 37% higher risk of all types of stroke, and a 44% higher risk of ischaemic stroke. Each serving of fried fish or fish burger per week was shown to increase the risk of a stroke by 10%, with a 13% higher risk for ischaemic stroke.

This research reveals a strong association with the method of preparation when considering relationships between fish intake and stroke risk. It also shows that despite the important role of dietary habits earlier in life, the risk of stroke may be influenced by dietary factors pursued beyond the young adulthood and middle age years.

Refs:
1. Calder PC. *Clin Sci*(London), 107(1):1-11, 2004.
2. Mozaffarian D et al *Arch Intern Med* 165(2):200-206, Jan 24, 2005.

Organic diet shown to have health benefits in rats

While organic food is widely considered to be healthier than food produced under conventional conditions, to date, few well designed investigations have been undertaken to evaluate the evidence to support this view. Measurement of the influence of organic versus conventional food on human health is hard to quantify, due to the difficulty in controlling the wide range of other parameters influencing health.

A team of researchers based at the Danish Institute of Agricultural Sciences, and the University of Newcastle in the UK, have published findings from a study during which rats were fed on a diet based either upon foods grown under organic cultivation, or with foods grown conventionally using either low or high levels of fertiliser, and pesticides, over a 44 week period. The diets consisted of potatoes, carrots, peas, green kale, apples and rapeseed oil, and had similar energy and protein contents, and a high content of fat compared to the recommended level for rats. Vitamins, minerals and amino acids were added to all three diets, and the rats received the same diets throughout their life.

The results found that rats fed on organic and minimally fertilised diets had a higher content of immunoglobulin G (IgG), and higher vitamin E plasma levels than rats fed on the conventionally grown diet. A tendency towards a lower weight and amount of adipose tissue in the rats fed organically, was also measured. It was also observed that rats (a nocturnal animal) fed the organic diet were more relaxed in terms of their daytime physical activity (measured using infrared sensors) than those fed conventional food.

The authors reported that in all cases, where differences were observed, there was a beneficial effect of the organically grown diet on the health of the rats. They concluded that this indicates a positive effect of organically grown compared to conventionally grown food, although cautioned that the very low level of fertiliser used in the organic foods needs considering, and that these results cannot be directly extrapolated from rats to humans.

The need for further interdisciplinary research in the area of human health aspects in relation to organic foods, was highlighted by the researchers.

Refs:
Lauridsen C et al, Danish Institute of Agricultural Sciences & Department of Agriculture, University of Newcastle.
www.darcof.dk/research/health.html

Spiders and beetles choose their foods wisely

While many herbivores and omnivores are known to adjust their food selection behaviour to regulate the intake of multiple nutrients, carnivores are generally assumed to be less selective, seeking to optimise their rate of prey capture above all other considerations. This perception has now changed however, with the recent discovery by Auckland University biologist David Raubenheimer and colleagues in Denmark, Britain and Israel, that spiders and beetles actually have the ability to choose their foods wisely.

Their study whose results were published in the January 7th issue of the journal *Science*, found that spiders actually pick and choose which flies and other insects they eat to ensure that they get the right balance of proteins and fats. This selection can take a number of different forms, including selection among foods of different nutritional composition, eating more of a prey if it is rich in nutrients that the predator is deficient in, or extracting specific nutrients preferentially from a single prey item.

Tests on humans by the same team have also found that we unconsciously choose a balance of proteins, fats and carbohydrates from a buffet. Specifically, we seem to be biologically "hard-wired" to eat at least a certain amount of protein, found in foods such as meat and dairy products, and usually not much more than that amount.

Refs:
Mayntz D et al, *Science*, 307(5706): 111-113, Jan 7, 2005.

Missing References for articles from Phytonews 20

Vioxx® withdrawn ***Pg 5***

Refs:
1. Merck announces voluntary worldwide withdrawal of Vioxx®. New Release, www.vioxx.co.nz/pdf/pressRelease.pdf
2. Medsafe website, www.medsafe.govt.nz/Profs/PUarticles/COX2info.htm
3. Mamdani M et al. *Lancet* 363(9423):1751-1756, 2004.
4. Clark DW et al. *Drug Safety* 27(7):427-456, 2004.

EU creates organic science network: ***Pg 11***

Refs:
CORDIS (Community Research & Development Information Service), http://publications.eu.int/cordis

Written by Phil Rasmussen. Edited by Noeline Jonkers

Published 4 times a year for customers of Phytomed Medicinal Herbs Ltd
P.O. Box 83068, Te Atatu South, Auckland 1008, New Zealand.

Subscriptions for non-customers: $28 per year for 4 issues