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Meta-analysis supports Astragalus as adjunctive treatment for lung cancer

Lung cancer is the most common cause of death from cancer in the United States, accounting for 27% and 31% of all cancer deaths in women and men, respectively[1]. Non-small-cell lung cancer makes up 75% of all cases of lung cancer, yet the surgical and chemotherapy treatments for this have both low efficacy and high toxicity.

Meta-analyses have shown that, compared with surgery alone, adjuvant chemotherapy reduces the death rate at two years by only 13%[2], and adjuvant chemo- and radiotherapy reduces it by 14%[3]. In recent years the addition of platinum-based chemotherapy drugs to standard protocols has increased 12 month survival rates by 5% and tumour responses by 62%, but at the cost of a significant increase in adverse effects such as haematologic toxicity, nephrotoxicity, nausea and vomiting[4]. These combined outcomes of poor rates of survival and quality of life, as well as serious drug-induced adverse effects, point to the need for new approaches to treatment methods of advanced non-small-cell lung cancer.

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PHYTOmed™ medicinal herbs ltd.
Manufacturers and suppliers of herbal extracts for practitioners
P.O. Box 83068.
Edmonton, Waitakere 0652,
Auckland, New Zealand
Tel (09) 828 0040
Fax (09) 828 0039
Freephone 0508 PHYTOMED (749 866)

Meta-analysis supports Astragalus as adjunctive treatment for lung cancer

Continued from the front page.

Many herbal medicines have now been shown to be useful as adjunctive therapies when combined with chemotherapy in the treatment of various cancers, but the evidence for this in most cases derives from animal rather than human studies (*see Phytonews* numbers 7, 17 & 18[5,6,7].).Of these phytomedicines, the herb *Astragalus membranaceous* is particularly prominent, being a common ingredient of Traditional Chinese herbal formulations often combined with chemotherapy in the treatment of lung cancer. While the rationale behind such use is generally regarded as being mainly to help reduce the level of bone marrow suppression associated with chemotherapeutic treatment, several immunomodulatory actions by Astragalus of direct relevance to cancer treatment have been shown. These include stimulation of macrophage and natural killer cell activity[8,9], and enhancement of the immune recognition of lung cancer cells by inhibiting production of T-helper cell type 2 cytokines implicated in the development of immunological tolerance to tumour progression[10,11].

One of the most positive studies undertaken in recent years, was a Chinese clinical trial involving an injection of Astragalus in patients with advanced non-small cell lung cancer in combination with platinum-based chemotherapy[12]. This study compared combined Astragalus and chemotherapy treatment in 30 patients with chemotherapy treatment alone in a control group of 30 patients. This resulted in a mean remission rate of 5.4 months in the treated group compared with 3.3 months in the control group, and a median survival period of 11 versus seven months. At one year following this treatment the survival rate was 46.75% in the combined treatment groups, compared to 30.0% in the chemotherapy-only treatment group.

Encouraged by this and the large number of other studies involving Astragalus-based herbal medicines combined with platinum-based chemotherapy, researchers based at the University of California in Berkeley have recently conducted a meta-analysis of randomised clinical trials to evaluate the efficacy of Astragalus in this situation[13].

No restrictions were placed on the publication language, and a total of 1,305 potentially relevant abstracts were identified in a systematic search by the authors. Of these, 92 studies were fully evaluated, after which 34 were considered to be rigorous enough and relevant to the context of platinum-based drugs combined with Astragalus, and therefore included in their meta-analysis.

A comprehensive evaluation of these studies reviewed the effect of Astragalus-containing preparations on patient survival rates (all 34 studies) and tumour response (30 studies), with a smaller number of studies looking at performance status data (12 studies). No significant effects were found for specific herbal formulas in reducing severe white blood cell, platelet or haemoglobin toxicity.

While commenting that most studies were of poor quality, and that they were therefore unable to make firm conclusions, the authors stated that their meta-analysis results suggest that combining platinum-based chemotherapy with Chinese herbal medicine in the treatment of non-small-cell lung cancer may increase patient survival, tumour response, and performance status, as well as reduce chemotherapy toxicity, when compared with treatment with platinum-based chemotherapy alone[13].

The main limitation identified in most studies was failure to describe the method of patient randomisation used. This was in most cases probably an unfortunate oversight on the part of the researchers involved, and continues to be a weakness of a large number of all clinical trials. More than 40% of all trials published in western medical journals in 2004 have apparently either failed to use adequate randomisation methods, or failed to report the method for concealment of allocation[14].

The authors of this meta-analysis ended their evaluation by calling for confirmation of these conclusions in rigorously controlled, randomised trials. Nevertheless, their overall positive appraisal provides one of the most convincing validations yet of the efficacy of Astragalus as adjunctive therapy to mainstream chemotherapy treatment of non-small cell lung cancer.

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Vitex anti-prostate cancer in vitro

The fruit of *Vitex agnus-castus* (Chaste tree) has a long history of being used for gynaecological conditions such as cycle disorders, luteal phase defects, mastodynia and premenstrual syndrome. Two *in vitro* studies over recent years however, have reported inhibitory effects on oestrogen-sensitive breast cancer cells[1], as well as a number of different human cancer cell lines including breast, ovary, stomach, colon, cervix, and lung carcinoma cells[2].

Promising findings have now been obtained from a Swiss study which looked at the effects of a *Vitex agnus-castus* extract on prostate cancer cell lines[3].

Three different human prostate cell lines representative of different disease states were used to test the effects of a concentrated hydroethanolic 7:1 strength extract of Vitex on cell proliferation, cell cycle distribution, and induction of apoptosis (cell death). These included both benign prostatic hypertrophy epithelial cells, and androgen-sensitive and androgen-insensitive prostate cancer cells. Two different methods were used to differentiate between cell viability and cell number/proliferation, and a range of methods were used to investigate cell death. All experimental methods used are established tools in the preclinical assessment of drugs for prostate cancer.

The prostate cancer cell lines were incubated with Vitex extract in different concentrations ranging from one to 30mcg/ml for periods ranging from 24 to 72 hours.

Vitex extract was shown to equally inhibit the growth of all three cell lines in a concentration and time-dependent manner, with some growth inhibitory effects detectable after 24 hours, but becoming more apparent over time.

The IC50 values (concentrations required to cause a 50% inhibition of growth) were 7 to 8mcg/ml after 48 hours treatment. Additional analysis using flow cytometry was undertaken to determine whether the inhibition of cell growth was due to apoptosis and/or cell cycle arrest. This revealed that the inhibitory effects by Vitex on prostate cell proliferation were due mainly to apoptosis, including activation of caspase enzymes, but also partly to a weak cytotoxic effect.

Due to their long latency period, benign prostatic hypertrophy and prostate cancer are suitable conditions for chemoprevention and therapy by phytotherapy. There are a number of phytomedicines for which evidence of such effects is now apparent, and their multiple phytochemical makeup and likely mechanisms of action implicates the possibility of a lower predisposition to the development of resistance, a growing problem with drug therapy.

This *in vitro* study provides encouraging evidence of the possible efficacy *of Vitex agnus-castus* in the prevention as well as treatment of benign prostatic hypertrophy, as well as prostate cancer, which is responsible for a large number of deaths annually. It also indicates that more than one mechanism of action is likely to be responsible for inhibitory effects of prostate cell growth, and provides a strong rationale for clinical studies in men with either condition as soon as possible.

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Hemidesmus for enterobacterial infections

Despite the development of antimicrobial drugs, infectious diseases account for approximately 25% of global mortality, and an alarming 45% of deaths in developing countries. Gastrointestinal pathogens such as *Salmonella, Listeria, Toxoplasma, Campylobacter and Escherichia coli*, account for a large percentage of food-borne infectious diseases in these as well as in developed countries. The diarrhoea that results from such bacterial, viral or protozoal gastric infections is estimated to account for 25% of deaths among children under the age of five years old in India and Indonesia.

While self-limiting diarrhoea is often the outcome of many of these food-borne diseases, severe invasive disease or prolonged illness may occur in immunocompromised individuals, and antimicrobial therapy is therefore indicated. This can result in the development of antimicrobial-resistant pathogens, and their subsequent transmission to humans as food contaminants.

Enterobacteria are transmitted through the oral-faecal route, and mostly reside in the intestine either as commensals or pathogens. Infection with them leads to either non-inflammatory diarrhoea due to toxin production, or inflammatory diarrhoea due to invasion and destruction of intestinal microvilli, which can lead to serious microangiopathy and haemolytic uraemic syndrome, and sometimes death.

The root of *Hemidesmus indicus* is widely used in Ayurvedia and other schools of medicine for a range of conditions including rheumatism, leprosy, impotence and skin infections, as well as by inhabitants of Orissa state in India for the treatment of diarrhoea and dysentery[1]. No scientific validation of antidiarrhoeal activity has occurred until recently however, when Indian researchers tested extracts of *Hemidesmus indicus* root for possible activity against several species of *Enterobacteriacea*, the major causative organisms of bacterial-associated diarrhoea[2].

Four different microbiological test methods were used to detect and measure activity of both a methanolic and chloroform extract of Hemidesmus, against various bacterial species. These included *Salmonella typhimurium, Shigella dysenteriae, Shigella flexneri, Shigella boydii, Shigella sonnei,* and *Escherichia coli.*

The bacterial strains used in these studies were also tested for their sensitivity to a variety of common antibiotics. Some level of resistance was measured in all strains, with the *Salmonella typhimurium* strains found to be multidrug resistant to tetracycline, rifampicin, ampicillin, erythromycin, chloroamphenicol and cephalothrin.

In a modified agar well diffusion and swab method, inhibition of the growth of all strains was measured in a dose-dependent manner. This activity was especially potent against *S. flexneri*, and least effective against *S. dysenteriae*, with moderate activity being observed against the rest of the bacterial species tested.

The extract was made using cold percolation then concentrated by evaporation, although to what level was not reported. Principal phytochemical constituents however were identified. As part of this, mineral content of the Hemidesmus extracts was measured, and the presence of copper, zinc, iron and manganese in levels ranging from 0.08 to 1 parts per million were reported in the methanol extract. Zinc supplementation has been shown to have therapeutic effects on acute and chronic diarrhoea as well as dysentery[3], and the authors speculated that zinc along with other unknown active constituents, may contribute to the antienterobacterial activity of *Hemidesmus indicus* root.

Earlier work has also shown a relatively weak water extract of Hemidesmus to increase the absorption of water and electrolytes from rat intestine, suggesting a possible indication for such a preparation as an ingredient of oral rehydrating salt solutions[4].

This study provides encouraging evidence for a potent antienterobacterial activity for *Hemidesmus indicus* root, and suggests its potential value as an alternative or adjunctive treatment to antibiotics, to treat diarrhoea and other food-borne disease caused by multidrug resistant strains. These include Salmonellosis as well as other forms of gastroenteritis.

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Reduced antibiotic resistance in humans linked to reduced usage in animals

The widespread use of antibiotics as feed additives for agricultural animals to promote growth and compensate for stressful and crowded growing conditions is becoming an issue of increasing concern. The possible contribution of such usage, particularly in poultry, cattle and pigs, to growing problems of antibiotic resistance in humans has been a topical issue of discussion amongst scientists, regulators and interest groups in the United States and Europe over the past few years. Many sources have urged bans on non-therapeutic and some therapeutic uses of animal antibiotics to protect human health[1,2,3].

High and increasing rates of resistance to the antibiotics vancomycin, erythromycin and methicillin, are causing concern in pig farming, and several recent studies provide evidence that certain antibiotic-resistant pathogenic strains of bacteria have been circulating through the food chain from farms to humans[4,5]. A Dutch study published last year for example, found the rate of methicillin-resistant *Staphylococcus* aureus (MRSA) among a group of 26 regional pig farmers to be more than 760 times greater than the rate in patients admitted to Dutch hospitals[5]. MRSA has also recently been found in horses and in persons who take care of them, and possible transmission from cats and dogs to humans has been reported[6,7].

Campylobacter species are the most common bacterial cause of foodborne disease in many countries, and in Australia alone approximately 277,000 cases of *Campylobacter* infection are estimated to occur annually[8]. Resistance to the fluoroquinolone and macrolide groups of antibiotics, has now emerged globally with many *Campylobacter* bacteria, following their routine use in the production of broiler chickens[9]. Increasing proportions of patients in Europe and the United States are being infected with strains of Campylobacter species exhibiting antimicrobial resistance. This adds to the burden of disease, with fluoroquinolone-resistant organisms being associated with more severe disease, and an increased likelihood of invasive disease and death[10,11].

The use of fluoroquinolone antibiotics in food-producing animals has been prohibited in Australia for a number of years now, due in part to such concerns. A recent study which measured the prevalence of fluoroquinolone resistance among *Campylobacter jejuni* isolates obtained from Australian patients, has reported some encouraging findings which lend support to this policy[12].

Australian researchers examined *C. jejuni* isolates collected from 585 patients who contracted the infection between September 2001 and August 2002, across various areas in five different Australian states. None of the patients had received fluoroquinolone antibiotic treatment within one month prior to becoming ill with *Campylobacter jejuni.*

Of these locally acquired *Campylobacter* isolates, only 2% were resistant to ciprofloxacin, a leading fluoroquinolone antibiotic. These rates were much lower than those observed for overseas-acquired isolates, where 64% were resistant to ciprofloxacin. Resistance to tetracycline was seen in 7% of locally-acquired isolates, compared with 55% of infection acquired overseas.

The Australian resistance rates also compared very favourably with those reported in other countries where these antibiotics are widely used in animals, and resistance occurs in up to 80% of cases.

While antibiotic resistance can arise from several different causes, these findings provide convincing evidence of low rates of antimicrobial drug resistance among Australian strains of *Campylobacter jejuni*, which probably reflect Australia's policy of prohibiting fluoroquinolone antibiotics for animal use. The authors concluded that "use of fluoroquinolones in food animals in other countries has increased the risk of resistance in *Campylobacter* isolates infecting humans".

Lowered rates of human *Campylobacter* fluoroquinolone resistance, probably due to avoidance of their use in animals, have also been reported in other countries where such antibiotic use is banned in animals. Sweden, where these have been prohibited since 1986, and Norway, where such use has never been permitted, have both reported low rates of fluoroquinolone-resistant *Campylobacter* infecting humans[13,14].

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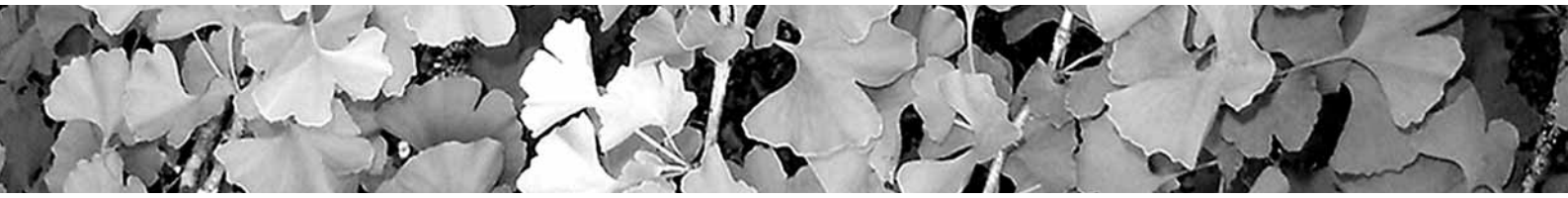
Withania for hypercholesterolaemia?



Withania somnifera **root is widely used in India for the treatment of a wide range of conditions, and anti-inflammatory, antitumour, antistress, antioxidant, immunomodulatory and hepatoprotective activities have been reported[1,2,3,4,5,6,7,8]. Hypoglycaemic and hypocholesterolaemic activities were first reported for the closely related species *Withania coagulans* in diabetic rats in 2004[9]. Findings published from two further studies involving hyperlipidaemic rats recently, provide further support for possible beneficial effects of both species in the treatment of hypercholesterolaemia[10, 11].**

In one of these studies, conducted by researchers at Sardar Patel University, Gujurat, India, food containing 750mg or 1500mg of *Withania somnifera* root powder was administered to both normal and hypercholesterolaemic rats over a four week period[11]. Various plasma lipid parameters were then measured, including total lipids, total cholesterol and triglycerides, as well as HDL, LDL and VLDL-cholesterol levels. The atherogenic index (AI, calculated as (total cholesterol – HDL cholesterol)/HDL cholesterol) was also estimated. Faecal cholesterol, neutral sterol and bile acids were extracted and estimated, and hepatic antioxidant status was evaluated through measurements of malondialdehyde, superoxide dismutase, catalase, and total ascorbic acid content.

Withania administration resulted in no significant differences in final body weight or food intake in all animals, however a small decline in liver weight occurred in both normal as well as hypercholesterolaemic rats. A reduction in total lipids, total cholesterol and triglycerides also occurred in both groups, effects in all cases being greater in rats with high rather than normal lipid levels. Significant reductions were also measured in LDL-cholesterol, VLDL-cholesterol, and the AI, while levels of HDL-cholesterol increased. These effects were more marked in animals treated with a higher dose of Withania, with total cholesterol falling by 40% after the lower dose, and 51% after the higher dose in hypercholesterolaemic animals, and 10% to 17% in normal animals. Hepatic total lipids, total cholesterol and triglycerides were also reduced in hypercholesterolaemic animals treated with Withania, and an increase in HMG-CoA reductase activity (responsible for cholesterol production) and bile acid content was observed in hypercholesterolaemic but not normal rats. Increased levels of faecal cholesterol, neutral sterols and bile acid content were observed following Withania administration in both normo-cholesterolaemic as well as hypercholesterolaemic rats, but were again more marked in the latter. Decreased hepatic malondialdehyde, and increased activities of catalase and superoxide dismutase enzyme activities, also occurred in the hypercholesterolaemic group.

In the second study, an aqueous extract of dried fruits of *Withania coagulans* (a related species growing naturally in Baluchistan in India) was given orally at a dose of 1000mg per kilogram to hyperlipidaemic rats for seven weeks. Serum levels of cholesterol, triglycerides and lipoprotein levels were then measured[10]. A preparation containing *Commiphora mukkul* (shown previously to be hypolipidaemic[12, 13, 14] was also given to two other groups as a reference treatment.

Following Withania administration, a 15% reduction in serum cholesterol, triglyceride and lipoprotein levels occurred in hyperlipidaemic compared with control rats, although no change in the AI, hepatic cholesterol and hepatic lipid peroxidation (LPO) was observed. Fewer degenerative and fatty changes in the livers of high fat fed and Withania-treated animals was also reported, these effects being similar to those of the *Commiphora mukkul* preparation.

Results from the first study indicate a marked hypolipidaemic and hypocholesterolaemic effect by Withania somnifera root, as well as beneficial effects through increasing HDL-cholesterol and antioxidant hepatic enzyme activities. The possible mechanisms of these effects are several, but are likely to relate at least in part to increased faecal excretion of cholesterol and bile acids. This could be attributable to the high fibre and phytosterol content of Withania root, estimated at 178mg per gram[15,16]. Increased hepatic bile acid production by hypercholesterolaemic animals is a further possible mechanism of action suggested by increased HMG-CoA reductase activities. Inhibition of hepatic lipid peroxidation by antioxidant components such as sitoindosides, withaferin A, flavonoids and vitamin C, could also contribute to antioxidant and anti-atherosclerosis activities, with additional protective effects against cardiac disease[17, 18]. Seeds of *Withania coagulans* contain β-sitosterol and linoleic acid, and these may be contributory to the hypolipidaemic activity observed in the study using this preparation.

While it should be noted that the doses used in both studies were many times greater than those normally taken by humans, these findings suggest the possibility of potential protective effects against high levels of cholesterol and other harmful lipids, by both Withania somnifera root and *Withania coagulans* fruit.

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Diet of cholesterol-lowering foods as good as statin drugs

It is well established that several dietary strategies have the ability to reduce elevated blood cholesterol levels, yet few studies have compared the effects of long term adherence to particular diets with those of cholesterol-lowering statin drugs. With several individual dietary components now known to help in the treatment of hypercholesterolaemia, it seems likely that combinations of these rather than monotherapy, could be at least as effective as other current treatments for this risk factor for cardiovascular disease.

In the United States, The National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the American Heart Association, recommend the use of functional foods or foods high in components that reduce cholesterol, as additional options which may enhance the effectiveness of cholesterol-lowering diets[1,2,3]. These ingredients include viscous fibres, soya protein, plant sterols, and nuts, and health claims indicating that they reduce the risk of cardiovascular disease are now allowed for foods containing them.

A group of nutritionists based in Canada, the UK and the USA, have previously conducted metabolically controlled clinical trials which indicate that a 28 to 35% reduction in LDL-cholesterol is possible through combinations of plant sterols, soy protein, viscous fibres and almonds[4,5,6]. They have now taken this approach further by studying a group of 66 hyperlipidaemic persons under 'real-world' conditions[7]. These individuals were instructed on a self-selected dietary portfolio of cholesterol-lowering foods, and left to obtain their own food then monitored over a one year period. As 29 of the participants had previously completed a previous metabolic study comparing the effect of the dietary portfolio with that of a statin drug (20mg daily of lovastatin), researchers were able to make a comparison between the effects of the *ad libitum* diet and the statin drug.

Participants were instructed to follow a low saturated fat (<7% of energy intake), low-cholesterol (<200mg/day) diet for two months prior to commencing the study, then seen a total of nine times throughout the one year period. To prevent dietary preparation, they were randomly recalled with two days notice during the fourth and fifth month of the trial, and blood samples obtained. Measurements of blood pressure and records of the diet and exercise regimen for the seven days prior to the clinic visit were also made, and compliance to the dietary recommendations assessed. The participants brought all foods from supermarkets or health food stores, apart from bread and sterol-enriched margarine which were provided.

In addition to their ongoing low-fat diet, participants were instructed to consume four primary components of the dietary portfolio, namely plant sterols from a plant sterol ester-enriched margarine; viscous fibres from oats, barley, psyllium, okra and eggplant; soy protein from soy milk and soy meat analogues, and whole almonds. They were also instructed to consume additional sources of plant protein and fibre in the form of dried legumes, and to eat the recommended five to ten daily servings of fruit and vegetables. Advice on eating a vegetarian diet without the use of dairy foods, eggs or meat was also given, but if egg products were used, egg substitute and liquid egg whites were advised. If meat or dairy foods were consumed, restrictions in the amounts and selection of low-saturate-fat options were emphasised.

At the end of the one year study, only two participants were following a vegan diet, and five were following a lacto-vegetarian diet. The remaining participants were following an omnivorous diet. Animal protein intake as a percentage of total calories was however reduced from 11.2% to 5.6%.

Analysis of the blood results for the 55 participants who completed the study, showed a statistically significant association between mean total compliance with the dietary protocol recommended and changes in LDL-cholesterol. Similar associations were also shown for intake of individual dietary components, including soy, fibre, and almonds.

A comparison with the LDL-cholesterol reductions seen after one year on the self-selected portfolio diet with those seen on the metabolic portfolio and statin treatments, revealed that the responses for the 32% of participants who achieved falls in LDL-cholesterol of more than 20%, were comparable to those they achieved in an earlier trial involving lovastatin taken under metabolically controlled conditions[5, 8].

The authors concluded that more than 30% of motivated participants who ate the dietary portfolio of cholesterol-lowering foods under real-world conditions were able to lower LDL-cholesterol levels by more than 20%, a response which was not significantly different to their response to a first-generation statin taken under metabolically controlled conditions.

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More on anti-diabetic effect of Cinnamon

As reported in *Phytonews 19*, favourable results have been obtained from a human clinical trial conducted in Pakistan, involving the use of Cinnamon bark for the treatment of Diabetes mellitus[1]. These findings have recently been confirmed by a group of Korean researchers[2].

A hot water extracted aqueous extract of cinnamon was used, and oral administration to this to diabetic mice took place in doses ranging from 50 to 200mg/kg, once daily over a six week period. Cinnamon administration was shown to lead to a significant fall in blood glucose levels in a dose-dependent manner. Blood readings were made at two, four and six weeks following daily cinnamon administration, and the hypoglycaemic effect peaked at two weeks after treatment begun, and remained almost constant after four and six weeks cinnamon administration. The highest dose of 200mg/kg had the greatest hypoglycaemic effect.

No changes in mice body weight or food intake occurred during cinnamon treatment, and positive changes also occurred in serum lipid levels were also measured. Serum concentrations of triglyceride decreased by 45% in cinnamon-treated mice, while those of HDL-cholesterol significantly increased. Serum insulin levels were also measured to be significantly higher in the cinnamon-treated mice.

Though an animal study, this report provides further support for the use of this inexpensive and readily available spice as part of the management of Diabetes mellitus, including in cases where insulin resistance has occurred.

The previous human study also reported favourable effects on serum lipids[3], while other work has found evidence of possible enhancement of the effects of insulin for cinnamon constituents[4,5,6].

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More human-to-human cases of Avian Influenza

In a rather alarming new development, seven members of an extended family in Indonesia have recently died following infection with the avian influenza H5N1 virus. The family cluster of cases occurred in the Kubu Sembelang village, Karo District of north Sumatra, and to date, the World Health Organisation and Indonesian health officials have been unable to find the source of the infection. The first member of the family to fall ill died of respiratory disease on 4th May, but no specimens were taken prior to her burial and the cause of her death has not been conclusively determined. However, as the clinical course of her illness was compatible with H5N1 infection, epidemiologists at the outbreak site have identified this woman as the initial case in the cluster[1,2].

Of the other six confirmed cases, three had spent the night of 29th April in a small room together with this woman at a time when she was symptomatic and coughing frequently. Other infected family members lived in adjacent homes, and all confirmed cases in the cluster can be directly linked to close and prolonged exposure to a patient during a phase of severe illness.

While other sources of exposure have yet to be ruled out, to date it seems likely that the initial case was contracted H5N1 from poultry, and that other family members were infected by her or other relatives in what is known as tertiary transmission. No other community members outside this family subsequently became infected.
This is the third and largest cluster of cases where a human-to-human route of infection seems to have occurred, the previous two instances being in Vietnam and Thailand (see *Phytonews 23*[4]).

Another aspect of this cluster that should be noted however was that in one of the seven victims, a 10 year old boy, the virus appeared to mutate, as shown by a change over time in the genetic analysis of the virus from samples taken from him. His father, however, who apparently contracted the virus from him and also died, did not pass it on to anyone else, and a dead-end chain of transmission thus occurred.

This family cluster of H5N1 infection does however highlight the dangers and risks of a highly virulent and potentially pandemic human-to-human form of H5N1, evolving in communities prone to crowding and poverty, where public health measures and access to appropriate antiviral medicines are likely to be far from ideal (see *Phytonews 21*[3]). Indonesia has seen a steady rise in H5N1 human infections and deaths (39 deaths in 51 reported cases), and the virus is endemic in poultry in nearly all of the country's 33 provinces. Failure of Indonesia to control avian influenza in birds, or raise enough of the estimated US$900 million it will need to tackle avian influenza over the next three years, is becoming increasingly worrying[5,6].

In another recent development, close contact with and de-feathering of infected wild swans has been shown to be the likely cause of exposure to H5N1 in two separate clusters of human cases in the Republic of Azerbaijan[7]. Six deaths resulted from the eight or nine confirmed cases, the first reported outbreak where wild birds rather than poultry were the probable cause of H5N1 infection in humans.

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Norway launches seed bank to safeguard crops

A rather unusual project aimed at protecting the world's crop supply through development of a global seed bank has recently been announced by the Norwegian government. Construction will soon begin on the Svalbard Global Seed Vault, located inside a mountain in Norway's remote Svalbard Islands, some 1000km from the North Pole, and 450km north of the Norwegian mainland. The Ministry of Agriculture and Food (MAF) in Norway, believes Svalbard is an ideal location for the seed bank because of its isolated location and permafrost, which will ensure that the seeds are stored at freezing temperatures even if the refrigeration systems designed to maintain the optimal -180°C should fail.

Seeds will be packaged in foil, and stored at such cold temperatures that they could last hundreds, even thousands or years, according to the independent Global Crop Diversity Trust, which will help run the vault. It will have thick concrete walls, and is scheduled to open and start accepting seeds from around the world in September 2007.

The seed vault is designed to protect the world's seeds in the event of catastrophes such as plant disease or other threats, such as global warming, natural disasters, or war. While around 1400 other seed banks are in existence around the world, most of these are national rather than international, and are vulnerable to shutdowns, natural disasters, war and lack of funds.

Up to three million different types of seeds will be housed in the seed vault, which is projected to cost US$4.8 million to build, and will be administered under the Nordic Council of Ministers.

The idea for a seed vault dates back to the 1980's, and was catalysed by the 2001 International Treaty on Plant Genetic Resources for Food and Agriculture. This established common rules for access to crop diversity and aims at conservation, sustainable utilisation and fair and equitable sharing of the benefits of such resources.

Ref:

http://www.nutraingredients.com/news/printNewsBis.asp?id=68547

Neuroprotective properties of Verbena

Vervain *(Verbena officinalis)* is a perennial plant found wild throughout much of Europe and North Africa, as well as China and Japan, and is used for a diverse range of conditions including dysentery, enteritis, amenorrhoea, anxiety and depression. Anti-inflammatory and anti-bacterial properties have previously been characterised[1,2,3], however other possible pharmacological activities have been poorly investigated to date.

The diverse traditional uses of Vervain lead a team of researchers in Hong Kong to hypothesise that this phytomedicine could have protective effects on cells of the central nervous system, and to undertake various *in vitro* tests to investigate this possible activity[4]. Cell cultures of cortical rat neurons were pre-treated with an aqueous Vervain extract then exposed to one of various different neurotoxins. These included the neurotoxin dithiothreitol (DTT), tunicamycin, UV irradiation, hydrogen peroxide, as well as β-amyloid (Aβ) peptide, known to be one of the toxic factors triggering neuronal death in Alzheimer's disease .

The cortical neuron cell cultures were pre-treated with an aqueous extract of Vervain in concentrations ranging from 25 to 150ug/ml for 1 hour, followed by the various neurotoxins. In another experiment, Vervain was applied to neuronal cells for a duration of 18 to 23 hours after their exposure to Aβ peptide for one or six hours.

The presence of Vervain at concentrations of 50 to 100ug/ml was associated with a marked reduction in the level of cell death seen in cells treated with DTT and Aβ peptide. No such protection was however measured for those neurons exposed to tunicamycin, UV irradiation and hydrogen peroxide toxicity.

In the post-exposure to Aβ peptide experiments, similar protective effects of Vervain against the neurotoxicity induced by accumulation of these peptides was seen. This took the form of a reduction in the number of apoptotic neurons and reduced destruction of the neurite network in Vervain-treated versus control cultures. The mechanism of this protective effect of Vervain against Aβ peptide neurotoxicity was subsequently related to attenuation of the increased phosphorylation of two stress-induced enzymes, JNK (c-Jun N-terminal kinase) and PKR (interferon-inducing kinase). Increased activity of PKR and JNK has been reported in post-mortem brain samples of Alzheimer's Disease sufferers.

These in vitro studies provide evidence of a preventative effect of Vervain against nerve cell damage and destruction in some situations, including where a risk of Alzheimer's disease exists. It should however be noted that the concentrations of Vervain extract associated with these positive outcomes, are likely to be considerably higher than those achievable in vivo following oral administration of normal doses to humans, thus very large oral doses of Vervain extract would probably need to be taken to produce such effects.

Of interest also is that methanolic extracts of another South American species of Vervain, *Verbena littoralis*, have also been reported to enhance the growth of nerve cell neurites *in vitro*, in the presence of nerve growth factor[5,6].

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Antispermatogenic effects of Albizia lebbeck

Evidence of possible antifertility properties of the Indian phytomedicine *Albizia lebbeck* has recently appeared following publication of results from a study with male rats[1]. These effects have been revealed by one of a number of studies undertaken in recent years with a view to identifying potential new contraceptive compounds from Indian plants.

A concentrated extract of *Albizia lebbeck* stem bark was prepared using 3.0kg of dried powdered bark to produce around 51g of extract, although the exact concentration of the final extract used and its phytochemical make-up was not provided by the authors.

Rats were treated with 100mg of Albizia bark extract daily for 60 days, then concentrations of sperm in their reproductive organs measured. They were also exposed to female rats during days 55 to 60, and mating behaviour recorded.

Treated rats showed significant reductions in both sperm concentration of testis and cauda epididymides, as well as sperm motility in the cauda epididymis. Weights of testis, epididymides, seminal vesicle and ventral prostate, were also significantly reduced, and plasma levels of testosterone were reduced by 46% in Albizia-treated rats. Mating behaviour was nil as compared to 100% for control values.

No influence of Albizia on red or white blood cells, haemoglobin, haematocrit and glucose in the blood, and cholesterol, protein, triglyceride and phospholipid in the serum was measured, implying that its effects to arrest spermatogenesis in male rats following large doses appears to be a relatively selective action of this Ayurvedic agent.

This is not the first study to report anti-fertility properties for Albizia, a report of a similar effect by a methanolic extract of the seed pods of this plant being made by the same authors in 2004[2]. A subsequent study involving oral administration of isolated *Albizia lebbeck* saponins at a dosage of 50mg/kg per day, which resulted in a 100% reduction in fertility of male rats, indicates that these compounds are likely to be contributory to these effects[3].

Despite these findings, the dose of Albizia extract used in these experiments was large, equating to around 20gm in an average weight adult male. With this extract being a highly concentrated preparation with a dried bark extraction ratio of probably around 60:1, it seems very unlikely that anti-fertility effects will be achieved in humans, unless massive doses are used. Further studies using lower doses are however indicated.

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Written by Phil Rasmussen. Edited by Noeline Jonkers

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PO Box 83-068, Edmonton, Waitakere 0652, New Zealand.