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Panax quinquefolium (American Ginseng)

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PHYTOmed™ medicinal herbs ltd.

P.O. Box 83068, Edmonton,
Waitakere 0652, New Zealand
P (09) 828 0040
F (09) 828 0039
www.phytomed.co.nz

American Ginseng Helps Schizophrenic Patients

Schizophrenia is an illness often incorporating a significant level of cognitive dysfunction and a wide range of memory impairments[1, 2]. These can have a major impact on the quality of life, the ability to problem solve, and the social skills of schizophrenic patients[3].

Despite the prevalence and severity of such cognitive dysfunction in a large percentage of schizophrenic patients, treatment options are limited.

While some evidence suggests that atypical antipsychotic drugs such as clozapine, respiridone and olanzapine may reduce cognitive dysfunction in some patients[4,5], data is limited and in other patients further memory deterioration occurs[6]. Also the anticholinergic side effects of many antipsychotic medications probably contribute to memory deficits observed in patients with schizophrenia[7].

American Ginseng *(Panax quinquefolium)* is a plant native to north America, which like the related Korean or Chinese Ginseng *(Panax ginseng)* is traditionally used to improve vitality, mental exhaustion from overwork, and a wide range of other indications[8]. Like *Panax ginseng*, a mixture of triterpenoid dammarane saponins termed ginsenosides or quinquenosides are generally regarded as the most significant constituents, although the type and makeup of these and other constituents differ between the two Ginsengs.

A group of researchers in Hong Kong have investigated the effects of a proprietary extract of American Ginseng on the working memory of patients with schizophrenia[9].

Sixty four participants aged 18-55 with stable schizophrenia who had undergone no significant change in medication or symptoms over the previous 3 months, took 2 capsules daily of placebo or an extract of American Ginseng equivalent to 500mg dried root, standardised for ginsenoside Rb1 and Rg1 content, alongside their usual drug medication for a period of 4 weeks.

Cognitive function was assessed at baseline using a range of neuropsychological tests. Immediate and delayed auditory memory were both assessed using a modified version of the Logical Memory Test of the Wechsler Memory Scale. The Verbal Fluency Test was used to assess participants' ability to name as many examples as possible from the category of 'animals' within 1 minute, and a version of the Continuous Performance Test was used as a computerised test for sustained attention.

Clinical symptoms of schizophrenia (both positive and negative), and depression were also assessed using standardised symptom rating scales both before and at the end of the 4 week treatment. Adverse effects were also recorded.

Working memory was assessed using various techniques, including the Letter-Number Span Test of the Wechsler Adult Intelligence Scale in which unstructured sequences of letters and numbers were presented orally and participants requested to name the numbers first in ascending order and then the letters in alphabetical order. A Visual Pattern Test involving how well participants remembered filled boxes in a grid when the stimulus was removed from sight was used for visual working memory.

At the commencement of the trial no significant difference was measured between the two groups in terms of overall cognitive profile or in working memory performance, severity of illness symptoms or medication side effects.

After 4 weeks treatment American Ginseng treated participants showed a significant improvement in Visual Pattern Test performance ($p<0.006$), unlike the placebo group in which there was no significant change. No significant improvement occurred in performance on the Letter-Number Span Test in the American Ginseng treated group, although the placebo group's performance in this test deteriorated significantly ($p<0.01$).

No significant change in positive clinical symptoms was observed during American Ginseng treatment, and depressive symptoms and akathisia were also similar. However, both negative symptoms and extrapyramidal side effects reduced ($p<0.029$ & $p<0.015$ respectively). While placebo treatment also resulted in a significant decrease in negative symptoms ($p<0.022$), no change occurred in positive symptoms, depressive symptoms or medication side effects after placebo treatment relative to baseline values.

The mechanism(s) of these favourable effects on working memory are unknown, although various influences on the cholinergic nervous system may contribute. Reduced cholinergic system function is contributory to learning and memory deficits[10-12], and cholinergic abnormalities are observed in schizophrenic patients, including those with cognitive dysfunction[13-15].

American Ginseng and ginsenoside Rb1 have previously been reported to reduce amnesia induced by the drug scopolamine in rats[16-18], effects probably related to increased acetylcholine release and choline uptake by nerve terminals, particularly in the hippocampus[17,19]. Increased mRNA expression of the enzyme responsible for acetylcholine synthesis, choline acetyltransferase, has also been shown in rat brains[13].

While an open label study in design, another study using the same American Ginseng extract found evidence of a possible facilitatory effect on memory function following two weeks administration in healthy individuals[20].

Taken together, these results suggest that the particular extract of American Ginseng used may exert positive effects on memory function in individuals with schizophrenia. They also suggest that American Ginseng has the ability to reduce the occurrence of extrapyramidal symptoms in patients on antipsychotic medications. An important finding given the high incidence and distressing nature of these unpleasant drug side effects.

Further trials involving use of this phytomedicine as an adjunct to antipsychotic drug medication in patients with schizophrenia are warranted.

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Echinacea purpurea

The Safety of Echinacea in Children

With the widespread popularity of *Echinacea* as an immune tonic, an appraisal of its safety in children is useful.

A huge variety of Echinacea preparations are available, and it is important to consider the phytochemical makeup, origin and dosage of the product involved. In particular, which parts of the Echinacea plant were used, at what stage of the plant lifecycle these were harvested (eg during flowering or dormancy), and whether other potentially contributory factors may have contributed to a potential adverse reaction.

Clinical Trial Findings

A total of five clinical trials involving use of Echinacea-containing products in children have been published in the peer-reviewed literature.

In the largest trial, 524 healthy children aged 2 to 11 years old were given an alcohol free liquid preparation made by reconstituting dried pressed juice of the above-ground herb of *Echinacea purpurea* harvested at flowering, for up to 3 courses for upper respiratory tract infections over a 4 month period. Adverse events were recorded by parents[1].

No statistically significant difference in the overall rate of adverse events

was reported in the two treatment groups. However, a higher incidence of rash occurred in children treated with Echinacea versus placebo (7.1% versus 2.7%).

Two children experienced the onset of croup symptoms after receiving a dose of Echinacea. These symptoms may have been an allergic reaction, or could have been a chance occurrence, croup being not uncommon in young children with upper respiratory tract infections. Large doses of alkylamide-rich products can also sometimes cause pharyngeal irritation in sensitive individuals.

Another 12 week study evaluated a formulation containing aerial parts of *Echinacea purpurea* and roots of *Echinacea angustifolia*, propolis and vitamin C, in a group of 328 children aged 1 to 5 years[2]. Adverse reactions were observed in 9 of the Echinacea treated children and 7 in the placebo group. All were transient mild gastrointestinal and palatability symptoms and did not require discontinuation of treatment.

Another trial involved a product containing the herbs *Andrographis paniculata* and *Eleutherococcus senticosus*, and expressed juice from freshly collected flowering *Echinacea purpurea*, for colds in 133 children aged between 4 and 11 years[3]. All treatments were well tolerated, although one Echinacea treated child developed urticaria.

In a further study, no statistically significant difference occurred in reported side effects between a group of 90 children aged 12-60 months treated with placebo or an ethanolic extract made using fresh roots and dried mature seeds of *Echinacea purpurea* or placebo[4].

No adverse effects were reported in a recent Italian clinical trial involving administration of an *Echinacea angustifolia* containing product to 37 children with recurrent pharyngotonsillitis or otitis media[5].

Adverse Reactions Reports in Australia and New Zealand

An enquiry to the Office of Product Review of the TGA in September 2011 produced a listing report of 97 adverse drug reactions for Echinacea-containing medicines received between April 1990 and June 2011.

Of the 97 cases, the actual medicine name and brand was sometimes not reported, and 15 involved Echinacea users of an unknown age. A total of 10 cases involved children aged 12 or under, and one case a child aged 13. Five involved children taking other medications apart from Echinacea. Urticaria was the most common reaction reported (3 cases), with two cases of bronchospasm, two of dyspnoea, one of erythematous rash, and one each of arthritis, diarrhoea, facial oedema, tremor, and hyperkinesia.

As at September 2011, the Centre for Adverse Reactions Monitoring (CARM) in New Zealand, had received a total of 11 adverse reactions reports to Echinacea products. These were 8 reports for Echinacea, 1 for Echinacea and Ester C, and 2 for Echinacea and Vitamin C[6]. Only one of these reports involved a child, this being a case of a 3 year old boy who died after choking on an Echinacea and Vitamin C tablet. A postmortem attributed this to the fact that the tablet was probably too large for a 3 year old to swallow; no blame was placed on the Echinacea component as such, at the time.

Summary

While there is a lack of robust and substantial data, a review of the published literature relevant to Echinacea use in children reveals little evidence that oral ingestion poses any risk of serious adverse effects.

The most common reported adverse effect appears to be a transient rash as a result of urticaria or atopic dermatitis. These are common manifestations of allergic or hypersensitivity reactions, produced in a small percentage of individuals by virtually all medicines.

Appraisal of these reports and the few clinical trials to date leads to the conclusion that allergic reactions occur in a small percentage of children, and appear more likely with products containing aerial parts. This is probably attributable to the presence of allergenic pollens and other constituents in flowering plant tops, not present or found in lower levels in the root[7-9].

Children with a history of atopic skin reactions, or sensitivities to the *Asteraceae (Compositae)* plant family, are probably more at risk from such reactions[10,11].

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Recent Research on Valerian

Valeriana officinalis (Valerian) root is a well known natural remedy for anxiety and insomnia, and has been widely used for sleep disorders. While like most herbal medicines its mechanism(s) of action is unknown, various modulatory effects on GABA-A (gamma amino butyric acid type A) receptors have been reported[1-4]. These receptors are also key sites of action for various psychoactive drugs such as benzodiazepines and anticonvulsants.

However, despite having a strong traditional reputation for helping with these conditions, not all clinical trials into the use of Valerian for insomnia have produced positive findings[5]. While several trials show a beneficial effect, some of these involved products containing Hops as well as Valerian[6-8], and others failed to find convincing evidence of a significant sedative action[9-11].

In his well known text 'Herbal Medicine', Rudolf Weiss, a highly esteemed German doctor who used herbal medicine widely during and after World War II, reinforced the need for adequate dosing of this herb. He states that "to be properly effective, Valerian has to be prescribed in a sufficiently high dosage. It is almost pointless to give ten or twenty drops of Valerian tincture; the dose has to be very much larger, at least a whole teaspoonful of the tincture….the single dose of one teaspoonful may, if necessary, be repeated two or three times at short intervals"[12]. A large percentage of published trials, however, have involved doses of 2 grams or less of dried root equivalent[9,11], and sub-therapeutic dosing may be a contributing factor to lack of efficacy. It is also of concern that several products used in these negative clinical trials either did not have their phytochemical levels measured and recorded, or contained levels of key compounds regarded by experienced phytochemists as being relatively low.

Good raw material quality is imperative for efficacious phytotherapy, and a further contributory factor to the failure of some products to achieve favourable results in clinical trials could be their relatively low levels of valerenic acid. This and related sesquiterpene compounds including acetoxyvalerenic acid and hydroxyvalerenic acids, all modulate GABA receptors and are generally regarded as the most important active constituents[1,2]. The extent of GABA-A receptor modulation has been related to the valerenic acid content of the product concerned[1].

While valerenic acid itself as well as acetoxyvalerenic and hydroxyvalerenic acids are generally assayed and collectively quantified as 'total valerenic acids' by herbal laboratories, a new study suggests that this may be inappropriate[13].

German researchers compared a Valerian extract high in valerenic acid content but low in acetoxyvalerenic acid levels, with one containing the same amount of total acids, but low in valerenic acid and high in acetoxyvalerenic acid. In an animal model of anxiety the Valerian extract with high valerenic acid but low acetoxyvalerenic acid was more effective than extracts with lower valerenic acid and higher acetoxyvalerenic acid contents.

While both these acids as well as hydroxyvalerenic acid bind to GABA-A receptors, it could be that acetoxyvalerenic acid inhibits rather than amplifies the anxiolytic activity of valerenic acid. More research is needed to further explore these allosteric differences which could also help explain the unsatisfactory outcome of many trials. In the meantime, it would seem that individual acid quantification and optimisation of pure valerenic acid levels in Valerian extracts could produce better clinical results.


Valeriana officinalis (Valerian)

Other potential applications of Valerian include symptomatic relief in dysmenorrhoea, protective effects against Parkinson's disease[14, 15], assistance with benzodiazepine drug withdrawal[16, 17], and the treatment of patients with Obsessive-Compulsive Disorder (OCD). A recent trial involving 31 adults with OCD who took Valerian or placebo for 8 weeks produced positive findings. In this Iranian trial, a daily dose of an extract equivalent to 5.5grams dried root produced improvement in obsessive and compulsive behaviours, with no evidence of any adverse effects[18].

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Rosemary Protects Against Ovarian Cancer?

Cancer is a main cause of morbidity and mortality in most industrial countries, and much research is taking place into natural products and their ability to have preventative or useful treatment activities in this disease.

Rosemary is a well known herb from southern Europe, now grown around the world, whose widespread traditional uses included as an antimicrobial and preservative against decaying meat. Research has revealed various pharmacological activities including antioxidant, antimicrobial and hepatoprotective properties[1].

Main active constituents include phenolic acids and flavonoids such as caffeic acid, rosmarinic acid, ursolic acid, carnosic acid and carnosol. Much of the antioxidant activity appears to derive from carnosol and carnosic acid[2,3].

Population based studies have reported an inverse relationship between consumption of Mediterranean herbs such as Rosemary, Sage, Parsley and Oregano, and development of lung cancer[4]. In recent years interest in the potential ability of Rosemary to protect against certain forms of cancer has increased.

Inhibition of carcinogen-induced mammary tumorigenesis by Rosemary[5] and skin tumorigenisis by Rosemary and its constituents carnosol and ursolic acid[6], were reported in the early 1990's. Subsequent findings from cell culture as well as animal studies have demonstrated the anti-cancer potential of Rosemary extract itself, as well as carnosol, carnosic acid, ursolic acid, and rosmarinic acid[7, 8]. Carnosol has been evaluated for anti-cancer properties in prostate, breast, skin, leukaemia, and colon cancer with promising results[9].

A recent Australian review on the subject of Rosemary and cancer prevention summarised results from 8 animal studies and 28 *in vitro* studies published between 1996 and 2010 involving Rosemary or its constituents in cancer[7]. While no human clinical studies were identified, the cumulative evidence suggests significant anti-cancer activities and protective effects of Rosemary on colorectal cancer and other forms of cancer.

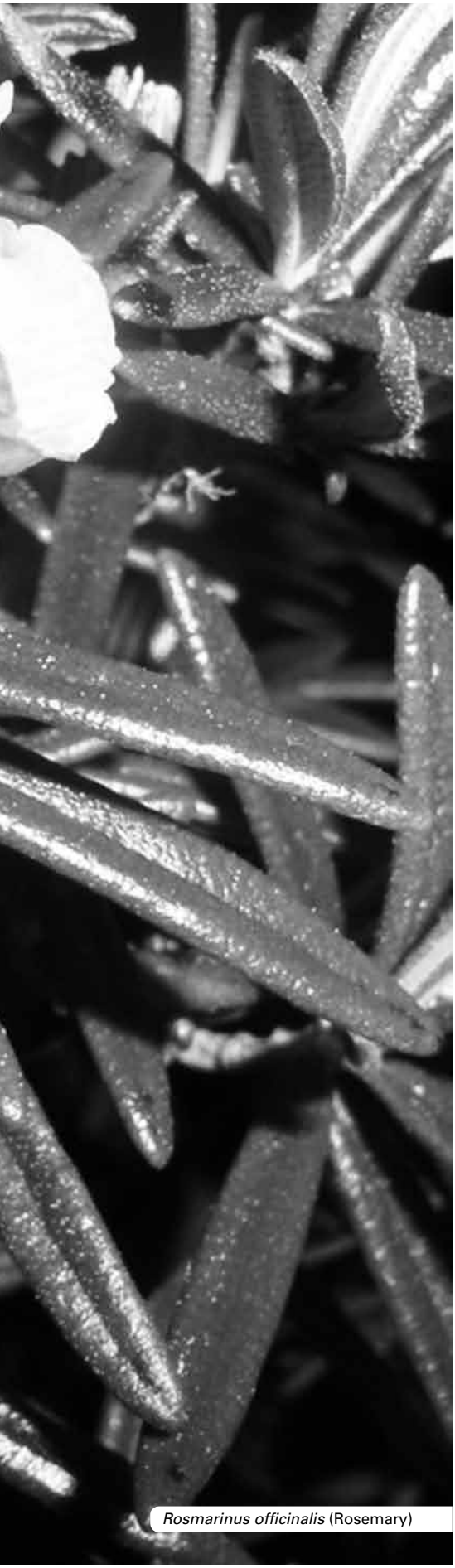
These anti-cancer properties appear to relate to molecular changes in the multiple-stage process of cancer development, and are not tissue or species specific. They are also dose related, an important finding in support of a clinical effect.

Ovarian cancer has a poor prognosis, often due to the recurrence of drug resistant clones following chemotherapy. Cisplatin is normally a first line chemotherapeutic agent, but its toxicity in cancer patients often limits the dosage that can be used.

The ability of cancer cells to develop multidrug resistance to chemotherapy is a major challenge to successful treatment of ovarian cancer patients. Several herbal medicines and their phytochemical components have shown promise in this regard, some through an ability to inhibit P-glycoprotein, the cellular efflux protein whose induction by cancer cells restricts cellular entry by cytotoxic drugs. These include constituents of Rosemary which have demonstrated inhibition of P-glycoprotein activity in multidrug resistant human breast cancer MCF-7 cells, and human cervical cancer KB-C2 cells[10,11].

Recent studies by Canadian researchers into the antiproliferation effect of Rosemary on human ovarian cancer cells *in vitro*, have produced some encouraging findings[12]. Antiproliferation effects of Rosemary extract and its bioactive ingredients were measured both alone and in combination with cisplatin on cisplatin sensitive and resistant ovarian cancer cell lines.

Both aqueous and ethanolic extracts of Rosemary were prepared and tested at dilutions ranging from 1 in 400 to 1 in 1200. Analysis showed that rosmarinic acid, carnosol and carnosic acid were major constituents of the 70% ethanol extract, while rosmarinic acid was the major one in the water extract.



Rosmarinus officinalis (Rosemary)

The ethanolic Rosemary extract showed a dose dependent antiproliferation effect on human ovarian carcinoma cells with an IC_{50} estimated at 1/1000 dilutions for the cisplatin sensitive cell line, although higher concentrations (IC_{50} of 1/400 dilutions) were required to kill the cisplatin resistant cell line. Relatively high concentrations of cisplatin were also required to inhibit this resistant cell line. However, when Rosemary extract was combined with cisplatin, a much greater level of cell proliferation inhibition was measured.

Carnosic acid, carnosol and rosmarinic acid were then tested in the same assays. While rosmarinic acid showed only weak activity, both carnosic acid and carnosol showed dose dependent antiproliferation activities between 2.5 and 20µg/ml. These concentrations are similar to those observed by other investigators using other human tumour cell lines[8,13].

The authors concluded that Rosemary extract inhibited the proliferation of ovarian cancer cell lines by affecting the cell cycle at multiple phases. Carnosol and carnosic acid also appear to arrest different tumour cells at different phases of the cell cycle, possibly through influencing the levels of different cyclins, and cell cycle regulatory genes.

While little is known about clinical pharmacokinetics of Rosemary phytochemicals in humans, the IC_{50} readings obtained in this *in vitro* study may not be far off actual plasma levels reached following oral administration of ethanolic Rosemary extracts. Rosemary contains around 5% combined carnosol and carnosic acid[6], and depending upon the dosage, therapeutically active plasma levels of these constituents could conceivably be achieved.

This study adds to others showing that Rosemary modifies the expression of multiple genes regulating apoptosis, and furthermore suggests that this common herb holds potential as a safe sensitising agent to enhance the efficacy of standard chemotherapeutic drugs.

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Artemisia annua Shows Anti-HIV Activity

Artemisia annua

Aerial parts of the medicinal plant *Artemisia annua* L. (Annual or Sweet Wormwood; Qinghaosu), have been traditionally used in China and nearby countries as a tea infusion to treat febrile illnesses and malaria.

The sesquiterpene compound artemisinin contributes largely to this antimalarial activity, and artemisinin and several synthetic derivatives are now used as antimalarial drugs. *Artemisia annua* is also now being grown and drunk as a tea in several parts of the world including Africa to help treat and prevent malaria[1].

A survey conducted in Kenya and Uganda between 2009 and 2011 revealed that more than half of *Artemisia annua* tea users had started taking it for other conditions apart from malaria. About half of such non-malarial usage was for the treatment of HIV/AIDS[2]. A survey of treatments prescribed by herbalists for people with HIV/AIDS in Cameroon, also found *Artemisia annua* to be one of the most frequently mentioned plants[3].

Based upon the above findings, a team of Dutch and Swiss natural product researchers investigated *Artemisia annua* for its *in vitro* anti-HIV activity[4].

Tea preparations were made of three different plants - *Artemisia annua*, the African species *Artemisia afra* and Rooibos (*Aspalathus linearis*). *Artemisia afra* has a similar phytochemistry to *Artemisia annua* but is not known to contain artemisinin[5], and was included to determine its contribution to any anti-HIV activity. The Rooibos tea was included as a negative control.

Nine different samples of *Artemisia annua* sourced from different locations in Africa and Germany were used, each quantified for artemisinin content. Tea infusions were prepared by addition of boiling distilled water, simmering for 3 minutes, then filtering while still hot. Anti-HIV analysis involved testing each sample at various dilutions to determine the IC_{50}, in a validated *in vitro* infection cellular system.

This involved two independent methods, the 'Infection format of "Fusion-induced gene stimulation", and the "dual-enhancement of Cell Infection to Phenotype Resistance" bioassay, which allow quantification of inhibitory effects of new chemical compounds or extracts[6]. The non-nucleosidic reverse transcriptase inhibitor drug Efavirenz, used clinically for the treatment of AIDS, was used as a positive control.

Artemisia annua tea infusions were found to be highly active in both bioassays for anti-HIV activity, with IC_{50} values as low as 2.0µg/ml. Interestingly, inhibitory activity was not correlated with artemisinin content in each sample, and pure artemisinin itself was found to be inactive at 25µg/ml. While as expected the Rooibos tea showed no activity, the *Artemisia afra* specimen had a similar level of anti-HIV activity to *Artemisia annua*. Activity levels of all *Artemisia annua* samples differed only moderately, indicating that the storage period and cultivation site of this plant do not appear to greatly influence the presence or levels of the active compounds involved.

These results provide evidence of anti-HIV activity not only for *Artemisia annua*, but also for *Artemisia afra*. This is of interest as a previous report exists of patients given *Artemisia afra* in combination with standard HIV drug treatment, and experiencing additional symptomatic improvement to those taking only standard drug treatment[7].

Contrary to initial expectation, these results also suggest that artemisinin plays no direct significant role in the anti-HIV activity observed.

The authors acknowledge limitations to their study, although they have now embarked upon a full metabolomic analysis (the study of metabolites as end products of cellular processes in cellular fluids of living organisms), to try and identify and quantify key components that may prove to be clinically active.

A substantial number of plant extracts have now been reported to possess *in vitro* anti-HIV activity, but relatively few clinical studies have taken place. Also, while some herbal medicines seem to be effective in reducing symptoms, generally no significant effect on antiviral activity

or enhancement of immunity has been shown[8-10].

The World Health Organisation has voiced concern that the uncontrolled use of tea infusions of *Artemisia annua* for malaria, particularly those with low artemisinin concentrations, may catalyse *Plasmodium falciparum* resistance. With HIV also, any such usage should ideally be controlled and monitored due to the serious nature of this disease.

However the incidence of HIV/AIDS in several countries is high, and due to various reasons including the inability to access drug therapy in some cases, a large number of patients with HIV in Africa and China are using traditional herbal medicines, particularly in regions where AIDS is endemic. These include patients taking concurrent anti-HIV drug medications, or those reliant on herbal treatments alone[11-13].

With AIDS now an enormous burden on the people, health systems and economies of many countries, there is an urgent need to rigorously evaluate promising herbal preparations such as *Artemisia annua* and *Artemisa afra*, for their potential beneficial effects.

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Ginger Beneficial in Diabetes-Related Infertility

Ginger has been used for medicinal as well as culinary purposes for centuries, and several of the alleged health enhancing properties associated with its traditional use are now being scientifically investigated[1].

Potential benefits in diabetes mellitus were first revealed by studies in hyperglycaemic rats and rats fed a high lipid diet[2]. These included reductions in blood glucose, serum total cholesterol, LDL, VLDL and triglycerides, and an increased HDL. No effects on blood glucose levels in normal male rats were measured in another study involving administration of a patented Ginger extract over a 64 day period[3]. However, dose dependent hypoglycaemic effects were then reported by a South African team in both normal and diabetic rats[4].

Oral administration of an ethanolic extract of Ginger (200mg/kg) to diabetic rats for 20 days produced comparable hypoglycaemic effects to those produced by a 25mg per kg dose of the oral hypoglyacaemic drug gliclazide[5]. Protective effects of an ethanolic Ginger extract against development of metabolic syndrome in rats, have also been reported[6]. Six weeks of a high fat diet produced increased body weights and blood levels of glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, free fatty acids and phospholipids, and all changes were reduced significantly by Ginger treatment.

A Korean study comparing the effects of dietary Ginger and Garlic in type 2 diabetic rats, found overall anti-diabetic effects of Ginger to be better than those of Garlic. The authors suggested that Ginger stimulates or modulates insulin activity, rather than being directly hypoglycaemic[7].

Interaction with 5-HT3 serotonin receptors involved in modulating insulin release has been suggested by another team as a possible mechanism of antidiabetic effects[8]. Ginger extracts also appear to inhibit α-glucosidase and α-amylase enzymes, key enzymes relevant to diabetes mellitus[9].

Possible applications of Ginger in diabetes have recently been further explored, through two studies involving male diabetic rats[10,11].

The first of these involved the effects of Ginger on fertility, using male rats rendered diabetic by alloxan injection. Rats were given either a methanolic or water extract of Ginger or vehicle for 65 days, then blood and semen samples were

collected[10]. The fertility index for each male was also calculated using a serial mating technique in which treated males were housed with untreated fertile females, and the percentage of females that became pregnant determined. Testicular and prostate gland weights, and the acute oral LD_{50} of both Ginger extracts used, were also determined.

Both extracts showed a very good safety profile, with calculated oral LD_{50}'s being 10.25 to 11.75 g/kg for the methanolic and water extract respectively.

After 65 days the fertility index of the diabetic control group was 55.56% and that in the normal rats 100%. Administration of the methanolic Ginger extract at doses of 100mg/kg and 200mg/kg per day increased the fertility index to 77.78% and 88.89% respectively, while the water Ginger extract at doses of 150 and 300mg/kg per day increased this to 66.67% and 77.78% respectively.

Both Ginger extracts also increased the weights of testes, seminal vesicles and prostate glands relative to the control diabetic group. Sperm motility and sperm cell counts were improved, and sperm cell abnormalities reduced. Histopathological examination of the testes of rats given Ginger extract showed less degeneration of spermatogenic cells than their control counterparts. Reduced serum total testosterone levels seen in diabetic rats were also increased in a dose dependent manner by both Ginger extracts.

Apart from direct hypoglycaemic and/or insulin modulatory effects, mechanisms for the enhancement in serum testosterone and improvement in motility and quality of sperm may relate to antioxidant as well as androgenic activities[12].

Another recent study investigated the effect of Ginger on oxidative stress markers in the mitochondrial fractions of various areas of the brains of diabetic rats[11]. A marked decrease in the antioxidant marker enzymes superoxide dismutase, catalase, glutathione peroxidise, glutathione reductase, reduced glutathione and increased malondialdehyde were observed in the brains of diabetic rats. Oral Ginger administration increased brain antioxidant defense mechanisms and downregulated malondialdehyde levels back to normal.

Diabetes mellitus and its complications is one of the leading causes of death in the world, and its incidence and impact on health services is forecast to dramatically increase in the future[13]. Together with other neurovascular complications, sexual dysfunction and infertility is an unpleasant outcome in a considerable percentage of both male and female diabetic patients[14].

While conventional treatment options such as sidenafil may be an option for some men, response rates can be low, and adverse effects may occur. Ginger, as a relatively cheap and readily available spice with a high safety profile, may help protect against the onset and reduce the manifestations of this diabetic complication. Human studies should now take place to further explore these potential benefits.

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Zingiber officinale (Ginger)

Andrographis a Useful Adjuvant to Cisplatin?

Cisplatin is an important anti-cancer drug used in the treatment of solid tumours especially for ovarian, testicular, cervical and small cell lung carcinomas. Its main action is to cause DNA damage and ultimately trigger apoptosis. As with other chemotherapeutic agents, drug resistance is a major obstacle to its clinical application[1].

Induction of the process of autophagy in human cancer cells by cisplatin has been implicated in recent studies as a possible pro-survival mechanism and thus contributing to cancer cell resistance to cisplatin-induced cytotoxicity[2-4].

Autophagy is a catabolic process by which cytoplasmic materials including damaged proteins and organelles are sequestered for lysosome-dependent degradation. Recent evidence suggests that autophagy is closely involved in the development of cancer, although its role is rather complex.

What seems to occur is during the tumorigenesis and oncogenic transformation processes autophagy acts as a tumour suppressor mechanism[5]. Once the tumour is formed however, autophagy in the tumour cells seems to provide a survival advantage to resist cell death induced by cancer therapy[2]. Suppression of autophagy is therefore being explored as a novel approach to the treatment of cancer and to help overcome the resistance of cancer cells to chemotherapy[2,6].

Herbal medicines are being increasingly evaluated for their possible benefits as adjunctive agents to be taken alongside anti-cancer drug therapy, and evidence is emerging of wide ranging potential applications for appropriately prescribed and monitored phytotherapy[7, 8].

Andrographis paniculata is a relatively cheap herbaceous plant widely used for centuries in India, China, Thailand and Malaysia to treat sore throats, influenza and upper respiratory tract infections. A highly bitter tasting plant, important active constituents are the labdane diterpenoids including andrographolide. Levels of andrographolide found in dried *Andrographis* range from around 0.5 to 6%[9].

These compounds have exhibited varying degrees of anti-inflammatory and anti-cancer activities in both *in vitro* and *in vivo* experimental models of inflammation and cancer[10,11]. A number of andrographolide derivatives are currently showing promise as potential new anti-inflammatory and anticancer drugs[12,13].

Previous research has shown that andrographolide is capable of sensitising human cancer cells to other cancer therapies such as TRAIL, doxorubicin, and 5-fluorouracil[14-16]. Encouraged by these findings, a research team in Singapore have investigated the effects of andrographolide on autophagy, and whether it has any influence on cisplatin-induced apoptosis[17].

In the first part of their study they determined that andrographolide is a potent autophagy inhibitor through disrupting the fusion of autophagosome with lysosome. These inhibitory effects of andrographolide on autophagy were independent of p53, an important tumour suppressor in human cancer.

Furthermore, cisplatin was observed to induce autophagy, and as previously reported[3, 4], this was shown to act as a pro-survival mechanism against cisplatin-induced apoptosis.

Finally, in both short-term apoptosis assays and long-term clonogenic tests, the addition of andrographolide was shown to markedly sensitise human cancer cells to cisplatin-induced cell death. These effects were also p53-independent, of relevance as cancer cells without a functional p53 appear to be more resistant to chemotherapeutic drugs.

A wide range of possible mechanisms for the direct anti-cancer effects of andrographolide have been reported, including inhibition of Janus tyrosine kinases-signal transducers and activators of transcription, phosphatidylinositol 3-kinase and NF-kB signalling pathways, suppression of heat shock protein 90, cyclins and cyclin-dependent kinases, metalloproteinases and growth factors, and the induction of tumour suppressor proteins p53 and p21. Multiple mechanisms may therefore be involved, including inhibition of cancer cell proliferation, survival, metastasis and angiogenesis[13].

What this latest *in vitro* study suggests is that andrographolide would seem to be an ideal compound to take as combination therapy alongside cisplatin, just as previous research has implicated similar benefits as adjunctive therapy with other cytotoxics including doxorubicin and 5-fluorouracil. Potentiation of the cytotoxic effects of cisplatin on a range of human cancer cells was measured in the Singapore study, adding to evidence of the direct anti-cancer effects of andrographolide.

Other possible benefits of *Andrographis* or andrographolide as adjunctive therapy in cancer patients receiving chemotherapy could include a reduction in drug-induced toxicity. Protection against cyclophosphamide-induced bone marrow and urothelial toxicity in mice has been reported[18-19].

At this stage it is inappropriate to extrapolate these results to presuming the same effects are achieved in a clinical situation involving oral administration of *Andrographis paniculata*, or andrographolide itself.

Oral bioavailability of andrographolide appears to have some limitations[20], although pharmaceutical chemists are currently working to develop formulations that should improve this[21].

Given the serious impediment of cancer cell chemoresistance to current drug chemotherapy, and the findings from this latest study, further research including clinical studies seem warranted.

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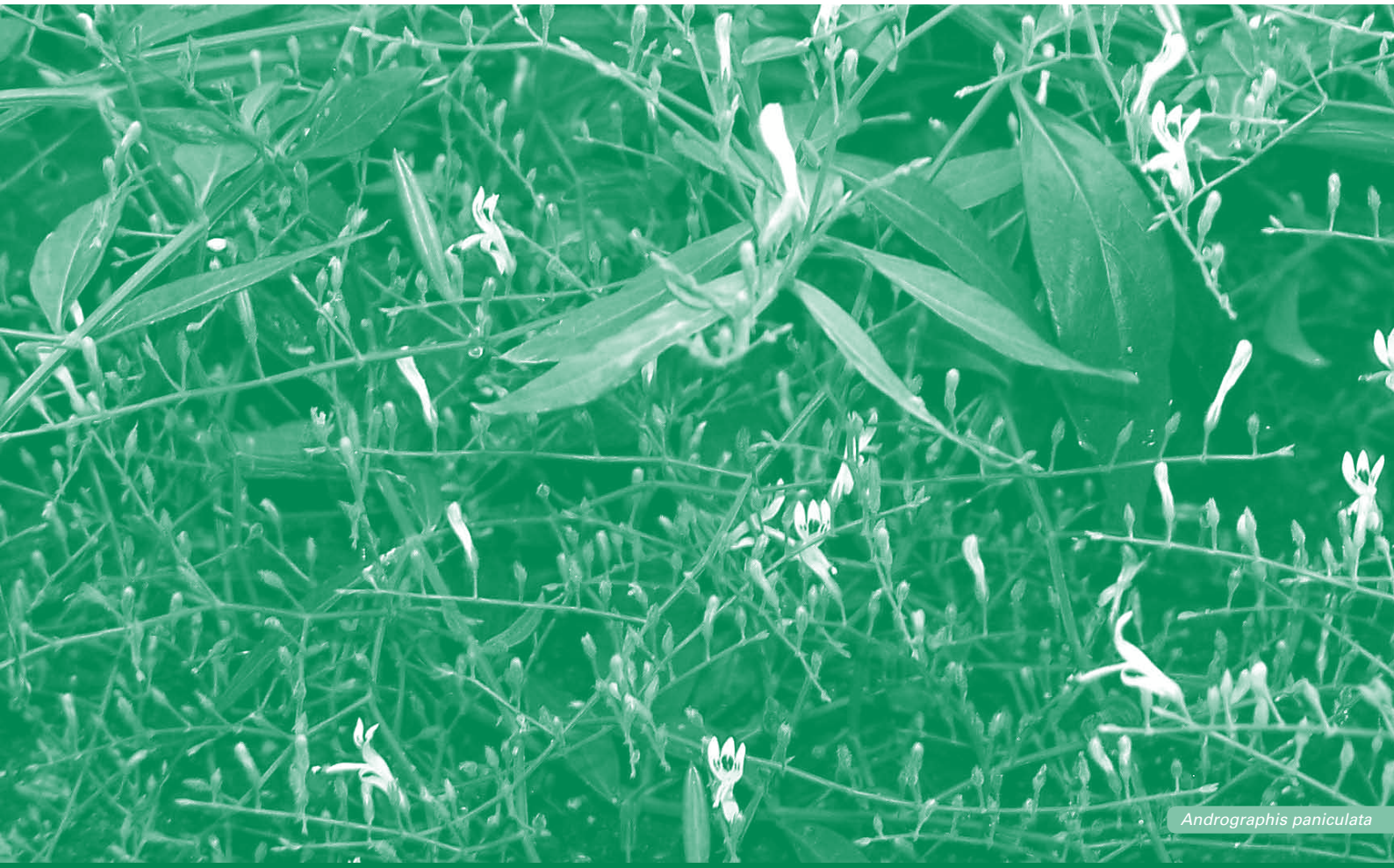

Andrographis paniculata

Written by Phil Rasmussen

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