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Comfrey ointment as effective as diclofenac gel for ankle sprain

Comfrey (*Symphytum officinale and Symphytum uplandicum*) is a plant with a long tradition of use for the topical treatment of acute painful musculoskeletal and joint complaints. As reported in *Phytonews 20* however[1], clinical trial validation of efficacy has until recently been lacking. This situation changed in 2004 when German researchers published results of a randomised trial involving application of comfrey ointment or a placebo ointment following acute unilateral ankle distorsions (sprains). This found a more rapid reduction in swelling and pain upon movement, as well as improved joint mobility, following comfrey ointment application over an eight day period[2].

A further trial has now been conducted by the same team of researchers, in which comfrey ointment was this time compared with a popular mainstream treatment for acute ankle sprain, diclofenac (Voltaren®) gel[3].

A total of 160 patients were included in the randomised study, the design of which was "investigator blind" rather than double-blind, due to the differences in appearance and smell for the comfrey ointment when compared to the diclofenac gel.

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The average age of the patients was 29 years, and all were of Caucasian descent. Each patient applied either comfrey or diclofenac four times daily over a seven day period. Treated skin areas were cleaned from every trace of the applied treatment prior to presentation to the investigator however, making it impossible for the treatment agent to be identified. As with the previous study, the trial involved patients presenting with uncomplicated, acute ankle sprains that had occurred within the previous six hours, either at the German Sport University in Cologne or one of two additional sports medicine clinics.

The primary measure of efficacy was the level of tonometrically recorded pressure pain (AUC, or Area Under the Curve of a graph of the pressure required to cause pain, versus the duration of treatment), and several secondary target variables were also measured according to published methods. These included ankle girth (swelling), pain scaling, evaluation of limitation of movement, and physician and patient's judgment of efficacy. Patients were examined on days 0, 4 and 7, and compliance monitored.

Both the comfrey ointment and diclofenac gel showed a potent effect in reducing the tenderness reaction, but patients treated with comfrey experienced less pain as shown by a statistically significant greater AUC than that measured in the diclofenac group ($p=0.046$). By the time of the third visit an overall good or excellent efficacy was recorded by physicians for 78% of patients in the comfrey group compared to 61% in the diclofenac group, while the efficacy reported by patients themselves was 84.2% in the comfrey group, compared to 70.8% in the diclofenac group. Both physician and patient assessments of these differences reached statistical significance.

This study provides further validation of the clinical efficacy of comfrey ointment in the treatment of acute sprains as a result of sports injuries, and furthermore implies a slight superiority of this treatment over one of the most popular synthetic drug treatments for such conditions.

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Effects of Echinacea on virus-induced respiratory cytokines

It is estimated that more than 200 viruses are responsible for causing the common cold, the most frequent type being rhinovirus which accounts for some 30 to 35% of adult colds[1]. Upper respiratory tract symptoms such as sneezing, sore throat and sinus congestion are commonly associated with such infections. However these symptoms, rather than being attributable to the direct effects of such viruses, are increasingly being regarded as the result of indirect effects produced as a result of the virus infection. Several studies in recent years have reported virus-induced increases in the transcription of certain inflammatory cytokine genes, and increased cytokine secretion from infected cells[2,3]. As many of these cytokines and chemokines function to attract inflammatory cells to the sites of microbial invasion[4,5,6], induction of pro-inflammatory genes has been increasingly regarded as a possible explanation for many typical symptoms associated with a common cold. Excessive and unrestrained release of such pro-inflammatory cytokines has also been implicated in the high level of virulence of the H5N1 avian influenza virus[7,8].

Echinacea preparations are often simplistically considered to produce effects known as 'immunostimulant', and are popular for the treatment and prevention of upper respiratory tract infections, including viruses such as the common cold or influenza. What is frequently under-recognised however, is that the traditional usage of Echinacea root preparations by various Indian communities in North America, often involved its application for conditions that were primarily inflammatory rather than infectious in nature, such as snake bites and major abscesses[9,10,11,12]. Anti-inflammatory effects for Echinacea have been reported using a range of experimental methods and inflammatory indicators[13,14,15,16,17,18,19]. Alkamides found particularly in the root of Echinacea purpurea and E. angustifolia seem to be particularly active as anti-inflammatory agents[15,19].

The effects of Echinacea on cytokine and chemokine secretion in both rhinovirus-infected and uninfected human epithelial cells, have recently been investigated by researchers based in the Department of Pathology and Laboratory Medicine, at the University of British Columbia, in Canada[20]. The effects on a variety of cytokines and chemokines following *in vitro* treatment with two different Echinacea extracts were measured, and some interesting results obtained.

Two commercial Echinacea preparations were used, one an expressed juice extract of the aerial parts of Echinacea purpurea, and the other a hydroethanolic tincture made using the root of this plant. Both extracts were concentrated then chemically characterised, and as expected, the juice preparation contained primarily polysaccharide components, while that made from Echinacea root contained alkamides and caffeic acid derivatives, such as caftaric, cichoric and chlorogenic acids. The human cell line used was a bronchial epithelial cell line known as BEAS-2B, and rhinovirus type 14 was used as the infecting virus.

Rhinovirus was added to the medium containing BEAS-2B cells, then incubated on a shaker platform at 34 °C for one hour. Unadsorbed virus and media were removed and the cells washed, then fresh medium added containing the relevant concentrated Echinacea extract, in concentrations previously shown to be non-cytotoxic. Duplicate cell cultures were removed at various times between 24 and 96 hours following infection, then assayed for 36 different cytokines and chemokines, using cytokine antibody arrays and an ELISA (enzyme-linked immunosorbent assay) method. Six different types of culture were used, namely uninfected or infected epithelial cells either treated or untreated, with one of the two Echinacea extracts. Echinacea treatment occurred over 48 hours, a time course previously shown to give good readings for most cytokines.

Rhinovirus infection was shown to induce or increase the secretion of at least 31 different cytokines and chemokines implicated as inflammatory mediators. These included in particular, the interleukins IL-1ß, IL-3, IL-5, IL-6, IL-17, granulocyte-macrophage colony stimulating factor (GM-CSF), interferon-gamma (IFN-γ), and tumor necrosis factor (TNF-α). Treatment of infected cells with both types of Echinacea however, reversed this stimulation of inflammatory cytokine and chemokine levels, either partially or completely.

In contrast to the above effects on infected cells, when uninfected cells were treated with Echinacea, cytokine levels were mostly increased, particularly by the root-derived preparation. The specificity of the Echinacea-invoked responses was validated through the inability of control extracts of St Johns wort *(Hypericum perforatum)* and American ginseng *(Panax quinqefolium)* to produce similar responses to those of the Echinacea extracts.

These investigations support an immunomodulatory rather than simple immunostimulant mode of action for Echinacea, whereby excessive and possibly damaging inflammation during a viral infection is reduced, yet the immune system is enhanced when Echinacea is taken in the absence of infection. A dual mode of action depending on the presence or absence of infection, and a possible explanation for the usefulness of Echinacea treatment during upper respiratory tract viral infection is therefore implicated. Such usefulness could also extend to highly pathogenic viral infections, such as that involving acute H5N1 (avian) influenza, in which excessive

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Inhibitory effect of Ginger against Influenza A virus

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activation of the immune response and a sudden and unregulated increase in the production of pro-inflammatory cytokines seems to occur[7,8,21] (see *Phytonews 23* for further discussion[22]).

In these experiments Echinacea root was associated with a greater immunostimulant response than Echinacea herb during the absence of infection. While a similar level of activity was shown by both Echinacea preparations on inflammatory cytokine release during rhinovirus infection, the limitations of this *in vitro* cell line study should be recognised. The bioavailability of immunomodulatory polysaccharides from the herb following oral administration is minimal, while that of alkamides from the root is relatively high[23,24].

These studies provide valuable information concerning the likely effects of Echinacea on the immune system during viral infection, and support its alleged beneficial effects as both a treatment or preventative agent. Further *in vivo* work to evaluate these cytokine-mediated effects in more detail are clearly warranted.

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Preparations of Ginger *(Zingiber officinale)* rhizome have been used for the treatment and symptomatic relief of influenza and colds for many centuries[1]. The well established warming (diaphoretic and circulatory stimulant) as well as anti-inflammatory[2,3] effects for this common phytomedicine and culinary herb are probably contributory to its apparent benefits in some cases of such upper respiratory tract infections. Potent antibacterial activity against a range of upper respiratory tract pathogens including *Streptococcus pyogenes/pneumoniaea* and *Haemophilus influenzae*, has also been shown[2,4,5].

Few studies on potential antiviral activity for Ginger have been reported however, apart from a Wellcome Research Laboratories commissioned bioassay which identified several sesquiterpenes with antirhinoviral activity in dried ginger rhizomes[6].

Japanese researchers recently investigated the effects of ginger on the growth of a strain of human influenza virus (influenza A/Aichi/2/68 (Aichi) virus), in a cell line of Madin-Darby canine kidney cells[7]. While a direct inhibitory effect on the virus infected cells was not observed in concentrations of 0.1 to 100 micrograms/ml, the ginger-conditioned medium of a murine macrophage (Mphi) cell line (RAW cells), did show antiviral effects, without cytotoxicity. These effects were accompanied by a gradual accumulation of tumor necrosis factor (TNF-α) in the ginger-treated medium, by its induction in the macrophages. This induction of TNF-α was shown to be associated with the anti-influenza effect of ginger, as such effects were reduced substantially when TNF-α was removed.

The results of this study indicate that ginger itself has little if any inhibitory effect on the growth of this type of influenza virus, but instead suggests the possibility of an anti-influenza action through potentiating the ability of macrophages to produce TNF-α, which is in turn toxic to the influenza A virus.

These findings, and the large amount of anecdotal evidence in favour of a beneficial effect of ginger during colds and influenza, support further investigations into its immunological and anti-inflammatory actions during such infections.

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Anxiolytic properties of Lemon Balm and Valerian

Lemon balm (*Melissa officinalis*) and Valerian (*Valeriana officinalis*) have both been used traditionally for the treatment of mild insomnia and anxiety. Valerian root has been investigated mainly as a sedative agent for insomnia, with most trials reporting positive outcomes[1,2]. Extracts of Lemon balm leaf have also been reported to increase self-ratings of calmness in healthy young volunteers[3,4].

Researchers at the Human Cognitive Neuroscience Unit in Newcastle upon Tyne in the UK, have now evaluated the effects of a fixed combination of both these herbs in the treatment of laboratory-induced stress[5]. A tablet containing the equivalent of 540mg dried Valerian root and 400mg Lemon balm leaf was given in different doses to a group of 24 young adult volunteers, prior to them undergoing a test to measure the response to stress. This test system, the Defined Intensity Stressor Simulation (DISS) computerised battery, involved the need for participants to attend to a series of challenging concurrent computer-generated tasks, such as mathematical processing and memory tests, and has previously been shown to increase self-ratings of negative mood, arousal and stress-related physiological responses[6,7]. Performance was evaluated with or without the herbal treatment, and testing occurred at one, three and six hours following herbal or placebo administration. A crossover design was used, in which all participants received each of three different doses on different test days, each separated by a seven day washout period.

Completion of the twenty minute DISS in the absence of treatment lead to a significant reduction in 'calmness' and increased anxiety. Administration of the lowest dose (600mg of extract or three tablets, containing the equivalent of 1620mg actual dried herb combination) led to decreased task-related anxiety at all time points commencing one hour post-dose. The highest dose used however, (1800mg of extract or nine tablets), resulted in a small increase in anxiety across all three post-dose sessions, although only reached statistical significance at a single time point. A mild reduction in task performance occurred at certain time points with the low and medium dose, but not the highest dose. This is consistent with the actions of a mild anxiolytic or sedative, and is likely to be attributable to the Valerian component of this preparation, as previous studies involving the same extract of Lemon balm alone have found it to either improve or have no effect on intentional accuracy[3,4].

This study provides evidence for anxiolytic effects for a combination of Valerian and Lemon balm during the face of a laboratory stressor, and is consistent with similar findings reported for both Valerian[8] and Lemon balm[7].

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Rosehips for Osteoarthritis

Osteoarthritis is a very common disease affecting an estimated 20 million Americans alone. It is characterised by joint pain and stiffness, particularly in the morning and evening, and after exercise. Apart from glucosamine, which, in some cases appears to help repair the damaged cartilage, most treatment is still largely symptomatic. This consists of non-steroidal anti-inflammatory drugs (NSAID's), aspirin, and steroids, all of which can result in serious side effects. Recent safety concerns resulting in the withdrawal in many countries of cyclo-oxygenase-2 (COX-2) inhibitor drugs, has further catalysed the need for millions of osteoarthritis sufferers to find safe but effective alternative treatment options.

Anti-inflammatory effects were first reported for a standardised dry powder made from seeds and shells of a subtype of rosehip *(Rosa canina)* by Danish researchers in 1999[1]. These included a reduced migration rate of polymorphonucleated leucocytes *in vitro*, and reduced plasma levels of C-reactive protein in humans, effects unrelated to the high vitamin C content of rosehips[2].

Several of the osteoarthritic volunteers who participated in these preliminary studies reported a dramatic reduction in pain symptoms during the treatment, and this lead to the same group of investigators carrying out a clinical trial involving rosehip for the treatment of osteoarthritis. Published in the July-August issue of the *Scandinavian Journal of Rheumatology* in 2005[3], some promising results were reported.

A total of 94 patients aged 38 to 92 years old, with diagnosed symptomatic osteoarthritis of the knee or hip, participated in this randomised, double-blind, placebo-controlled, crossover trial. Patients were recruited from outpatient clinics at the Department of Rheumatology of Copenhagen University Hospital in Glostrup, and the Institute for Clinical Research at Vejle and Copenhagen. Patients who had taken glucosamine sulphate and/or chondroitin sulphate, or the intra-articular drug hyaluronate or systemic or intra-articular steroids in the six weeks preceding enrolment, were excluded.

Each patient received either the placebo or active medication over a three month period, then were directly crossed-over to the other treatment for a further three month period. A dosage of five grams of rosehip powder was taken daily in the form of five capsules, each containing 500mg of a powder standardised for vitamin and mineral content. While patients using NSAID's regularly were advised to continue using the same dosage during the entire study, they were told to reduce intake of other analgesics if possible, after the first three weeks of treatment. Analgesic consumption was recorded daily, and this used as one of the outcome measures. Other outcome measures consisted of a validated disease-specific questionnaire (the WOMAC score) concerning severity of joint pain, stiffness, limitation of physical function, and patients' global assessment of disease severity.

Following three weeks of rosehip treatment, WOMAC scores for joint pain declined from 33.7 (± 19.4) to 29.4 (± 18.3), compared to a change from 33.7 (± 19.4) to 35.3 (± 21.5) for the placebo group, a change that was statistically significant. After three weeks of rosehip treatment, 82% of patients reported at least some reduction in WOMAC pain, compared to a 49% reduction in the group treated with placebo. After three months of treatment the same pattern was observed, although unlike the improvement seen during the first three weeks, this was less pronounced and failed to reach statistical significance. WOMAC scores for stiffness, limitation of physical function, and patients' global assessment of severity, all showed significant improvements during the three month active treatment period. The intake of paracetamol as a top-up 'rescue medication' by patients during rosehip treatment lessened by 40%, and use of mild synthetic opioids also reduced. The authors suggest that this patient-instigated reduction in intake of additional painkillers during active treatment may explain the lack of significance when pain was evaluated after three months of treatment.

A mild carry-over effect was also implicated from the observation that the improvements seen during active treatment did not completely reverse during the following placebo treatment period. The dropout rate was seven patients in each of the placebo and active treatment groups (most being due to perceptions of lack of efficacy), and the frequency of milder unwanted side effects was similar in both groups.

This study was well designed and suggests that five grams per day of the particular Scandinavian subtype of cultivated rosehip powder is safe and can reduce osteoarthritic pain to an extent that can enable the intake of additional analgesic medication to be reduced. Questions remain however as to whether this was the optimal dose for such conditions, and whether other varieties of rosehip possess the same activity. A longer term clinical trial involving greater patient numbers would also be useful.

This is not the first trial to evaluate the efficacy of rosehips in patients with osteoarthritis. Favourable results were also obtained from an earlier Norwegian study in which treatment with a dose of five grams daily of the same variety of rosehip was given to patients on a waiting list for either hip or knee surgery due to osteoarthritis. In this trial also, improvements were reported in joint mobility and joint pain following four months rosehip treatment[4].

A further stamp of approval to the evidence to date of rosehip being useful for the treatment of osteoarthritis has been provided recently in the form of a systemic review of clinical trials involving rosehip preparations. The German and Australian authors of this review, published in the January 2006 issue of *Phytotherapy Research*, concluded that while further confirmatory studies are required to prove this effectiveness beyond any doubt, moderate evidence exists for the use of a powder of the seeds and husks of a rosehip subspecies in patients suffering from osteoarthritis[5].

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Ginkgo for Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating neurological disease afflicting young and middle-aged adults. Demyelination of nerves results in problems with coordination, strength, cognition, mood, and sensation. Its rate of progression varies widely, and the availability of efficacious conventional medical treatments is unfortunately limited.

While approximately one third of MS patients use complementary medicine[1,2], few scientific investigations have taken place to assess the efficacy of specific treatments in this unpleasant illness. Since improvements in memory, depression, anxiety, concentration, fatigue and dizziness associated with cerebral insufficiency have been reported for Ginkgo biloba, and as these are all common symptoms of MS, American researchers decided to investigate ginkgo's ability to improve symptoms of this illness. They carried out a pilot clinical trial involving 21 MS patients who were treated with placebo or a standardised extract of ginkgo, and a number of the participants experienced favourable results[3].

All participants had been diagnosed with clinical definite MS as defined by recognised criteria. Those who had an exacerbation of their illness within four weeks of participating in the study, or who had been diagnosed with other neurological or psychiatric disorders, or who were taking various medications including other complementary therapies, were excluded. A total of 12 patients who received ginkgo and nine subjects who received placebo according to a triple blind procedure were evaluated. The ginkgo tablet used was a well known brand standardised to contain 14.4mg ginkgoflavone glycosides and 3.6mg terpene lactones (60mg extract) and a dose of four tablets daily (i.e. 240mg of extract) was taken for four weeks. No side effects or adverse events were reported or observed throughout the study.

Patient assessment before and after the treatment period was comprehensive, and involved completion of five separate questionnaires to assess patient symptoms. A variety of statistical methods were used to analyse the data obtained.

The results suggested a significantly greater improvement in individuals in the ginkgo versus placebo group, in particular, lower levels of fatigue. Improvement in four or more measures was only seen in the ginkgo group, but the existence of considerable individual variation in response to ginkgo (i.e. responders and nonresponders) was implicated.

The authors concluded that this pilot study showed very modest beneficial effects for ginkgo among some individuals with MS, but recommended the use of larger sample sizes and other methodological changes in future studies to evaluate its effects. These should include recognition and analysis of the apparent existence of "positive responders" and "negative responders", and perhaps a longer duration of treatment.

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Corydalis to improve memory and cognition

Alzheimer's disease is thought to be associated with defective function of the cholinergic nervous system, as patients with this form of dementia have decreased levels of acetylcholine (ACh) in brain areas related to memory and learning. Several drugs and phytomedicines with the ability to enhance brain acetylcholine levels by inhibiting its metabolising enzyme acetylcholinesterase, have been shown to have some benefits in the treatment of Alzheimer's. Lemon balm *(Melissa officinalis)* and Sage *(Salvia officinalis)*, are two such phytomedicines for which both memory enhancing as well as anticholinesterase activity has been reported, in recent years[1,2] (see *Phytonews 16 & 17*[3,4]). Significant acetylcholinesterase inhibitory activity for the Turkish plant Corydalis solida has also been reported[5].

A screening programme involving various plants used in traditional Danish herbal medicine, as well as three Corydalis species used in other forms of folk medicine for the improvement of memory and cognition, has recently been conducted by researchers based at the Danish University of Pharmaceutical Sciences in Copenhagen[6]. A total of 15 different plant extracts were tested for acetylcholinesterase inhibitory activity, using the Ellman colorimetric method.

A significant and dose-dependent inhibitory activity was measured for extracts of all different species of Corydalis, including *Corydalis cava*, *Corydalis intermedia*, *Corydalis solida* ssp. *laxa*, and *Corydalis solida* ssp. *slivenensis*. Both aerial parts and tubers of these species were assayed separately, with tubers showing more active enzyme inhibitory effects than the herbs. Activity was attributed to several compounds, but is likely to be particularly related to the protoberberine- and protopine-type alkaloids known to be common constituents of Corydalis species[7,8].

Of the other herbs tested, aqueous and methanolic extracts of *Ruta graveolens* (Rue), and methanolic extracts of *Lavandula angustifolia* (Lavender), *Rosmarinus officinalis* (Rosemary), *Petroselinum crispum* (Parsley) and *Mentha spicata* (Spearmint) showed moderate inhibition of acetylcholinesterase. This activity was however, considerably weaker than that shown by the Corydalis extracts.

The concentrations of Corydalis extracts required to produce more than 50% acetylcholinesterase inhibition in this *in vitro* study were in the region of 0.025mg/ml, however the likelihood of such levels being achieved with the brain following oral administration in clinical practice remains unknown given the lack of information about the pharmacokinetics of Corydalis or its constituents. This study nevertheless provides some support for the traditional uses of Corydalis tuber extracts from both Asia as well as eastern Europe as treatments for memory dysfunction.

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Cognitive effects of Sage

Memory and mood enhancing properties for the leaves of Sage *(Salvia officinalis)* have been described in several old European texts[1,2,3]. Activity as a cholinesterase inhibitor has also been reported for Sage leaves[4,5], and a placebo-controlled clinical trial conducted in Iran found improvement in cognitive function in patients with mild to moderate Alzheimer's disease following a four month treatment with three grams per day of a 1:1 strength sage leaf extract[6] (see *Phytonews 16*[7]).

British researchers have now conducted a double-blind, placebo-controlled, crossover study to investigate the effects of single doses of sage leaf on mood, anxiety and performance in a group of 30 healthy young participants[8]. As with the trial involving Valerian and Lemon balm previously reported, a Defined Intensity Stress Simulator (DISS) computerised multitasking battery of tests was used as a measure of laboratory-induced stress. Doses of 300mg and 600mg dried sage leaf were given on three separate days, seven days apart, to each participant, and assessments made prior to each dose, then at one and four hours after dosing. Mood assessments took place before and after the 20 minute performances in the DISS battery.

Both doses of sage were found to result in an improved mood even in the absence of the DISS stressor, with the lower dose reducing anxiety and the higher dose increasing 'alertness', 'calmness' and 'contentedness' according to the Bond-Lader mood scales. Performance in the DISS battery was however associated with a reversal of the anxiolytic effect of the lower dose, and a reduction in alertness during the test tasks undertaken. The higher dose however, resulted in an improved task performance relative to placebo.

In a concomitant investigation, the researchers also investigated the cholinesterase inhibiting properties of the sage extract. Their results confirmed those of previous studies, with a significant and dose-dependent acetylcholinesterase inhibitory effect being measured.

This study supports the potential benefits of this common and easily grown herb in both elderly patients as a preventative or treatment for mild dementia, as well as in healthy younger individuals, to improve cognitive functioning. In both situations, a dose dependent effect is likely, with higher doses being likely to produce the most favourable results.

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More on anti-nausea properties of Baical Skullcap

The antiviral protease inhibitor drug ritonavir, is used in the treatment of HIV, but unfortunately is often not well tolerated. The incidence of gastrointestinal disturbances such as nausea and vomiting is particularly high, with approximately 23% of patients experiencing these unpleasant side effects during therapy[1,2,3]. Alleviation of ritovavir-induced nausea could significantly increase patient compliance to this drug, thus boosting its antiviral effect and improving patient quality of life.

A reduction in chemotherapy-induced nausea has previously been suggested for the Chinese herb Baical skullcap (*Scutellaria baicalensis*), using a rat model designed to test anti-nausea activity[4](see *Phytonews 17*[5]). Following pre-treatment with an extract of Baical skullcap at doses of 1mg/kg and 3mg/kg, a significant decrease in cisplatin-induced pica (consumption of extraordinary articles of food) and kaolin intake was observed, suggesting an anti-nausea effect.

The same team of researchers at the University of Chicago, have now repeated their experimental method to investigate the effects of Baical skullcap (*Scutellaria baicalensis*) on ritonavir-induced nausea[6]. Ritonavir at doses of 20mg/kg caused a significant increase in kaolin consumption, but this was significantly decreased by pre-treatment with an aqueous extract of Baical skullcap, in a dose-dependent manner. The authors concluded that the antioxidant effects of Baical skullcap probably contributed to its anti-nausea effects in this animal model, and that antioxidant herbs may have therapeutic potential in ritonavir-induced emesis in AIDS patients.

While the results from this and their previous study using the chemotherapy drug cisplatin are supportive of such an effect, failure of the investigators to measure plasma levels of ritonavir or cisplatin in rats either treated or untreated with Baical skullcap is a weakness of both studies. While perhaps unlikely due to the intraperitoneal method of administration of Baical skullcap 30 minutes prior to each ritonavir administration by oral lavage, it remains conceivable that some kind of pharmacokinetic interaction between this phytomedicine and ritonavir in which plasma levels and thus side effects of ritonavir were reduced, could have contributed to these results.

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Toxic effects of BZP-based party pills

So-called 'party pills' have become very popular during the past two years, and are widely advertised and promoted in the public domain as being safer 'natural' alternatives to drugs such as ecstacy (MDMA or methylenedioxymethamphetamine) or amphetamines. Primarily taken for their ability to increase alertness as well as elevate mood and energy, they are also used for physical training.

While frequently termed 'herbal' party pills, the principal ingredient in most of these products in New Zealand is 1-benzylpiperazine (BZP), a totally synthetic substance. A similar compound, trifluormethylphenylpiperazine (TFMPP) is sometimes mixed with BZP in an attempt to produce psychoactive effects similar to those of MDMA (methylenedioxymethamphetamine or 'ecstasy').

BZP is a sympathomimetic agent which has stimulant effects similar to those of dexamphetamine. While its potency is less than that of dexamphetamine[1], a study involving former amphetamine addicts found equipotent doses of BZP and dexamphetamine to be indistinguishable[2]. BZP is a schedule 1 controlled substance in the USA[3] and is controlled in all states of Australia. In New Zealand however, an evaluation of BZP by an Expert Advisory Committee on Drugs presented to the Ministry of Health in April 2004, concluded that there was inadequate information about this substance and at the time put stronger controls on its distribution[4]. In July 2005 BZP was placed on a new schedule of controlled but not banned substances, making it legally available for sale to adults over 18 years of age. BZP is available in dose packages ranging from 70mg to 1000mg, and it is estimated that more than 8 million doses of BZP have been sold in New Zealand to date[5].

An increased frequency in weekend presentations to hospital emergency departments of patients experiencing adverse and toxic effects from these pills has occurred during the past two years. A study undertaken by clinicians at Christchurch Hospital's Emergency Department whose results were reported in the 16th December 2005 issue of *The New Zealand Medical Journal*, discusses toxicity concerns for BZP based upon the number and type of hospital presentations of patients experiencing adverse effects through taking party pills[6].

During a five month period from 1 April 2005 to 1 September 2005, all presentations associated with party pill use were examined. Urine or blood tests to confirm the presence of BZP or other illicit substances were undertaken in selected cases with severe toxicity. A total of 61 patients aged between 15 and 36 years attended a total of 80 occasions with adverse effects after ingestion of party pills. Alcohol was coingested in 39 cases, marijuana in 12, and nitrous oxide in 10. Multiple drug ingestion including MDMA, LSD and methylphenidate (Ritalin®), was involved in four cases. Females were 30% more likely than males to present with adverse effects, possibly a reflection of their relatively lower body weight and relatively higher dose taken.

The most commonly reported symptoms were palpitations, vomiting and agitation, with others including anxiety, headache, confusion, collapse, and seizures. Seizures occurred in 14 patients after BZP use, ranging from 30 minutes to eight hours following reported ingestion. A 16 year old female experienced five bouts of seizure several hours after taking four party pills without alcohol or other drugs, and a 25 year old male had a tonic seizure while driving a car which nearly led to a head-on collision, three hours after taking two party pills. Two patients displayed airway compromise and metabolic

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Toxic effects of BZP-based party pills

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derangements (metabolic and respiratory acidosis) deemed to be potentially fatal.

In March of last year, a 29 year old man in good physical health died from heart failure after a night of alcohol mixed with at least three or four party pills. The pathologist report found that lack of blood to the heart, probably secondary to an irregular heartbeat from raised ephedrine levels, was the likely cause of death[7]. Case reports of fatalities following ingestion of a combination of ecstasy or amphetamine and BZP have also been made[8,9].

While many users do not suffer significant adverse effects from taking BZP-based pills, the results from this study indicate the potential for this substance to cause unpredictable and serious toxicity in some individuals. Based on their results, the authors recommend that patients with seizure disorders, psychiatric illness or coronary disease should avoid BZP, as should those taking prescription sympathomimetics or anticholinergics (prescription antidepressants). Co-ingestion with MDMA or amphetamine should also be cautioned against.

The current regulatory status of these substances in New Zealand, allowing them to be manufactured without any requirement for quality assurance, and sold openly in poorly packaged and labelled containers to anyone over the age of 18, seems inadequate when a full appraisal of safety issues is made. The widespread availability and legal nature of party pills has furthermore encouraged a culture of stimulant pill used being regarded as normal behaviour at parties and concerts. A review of the available evidence on the safety of BZP is planned by the Drug Policy Unit at the Ministry of Health in 2006.

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