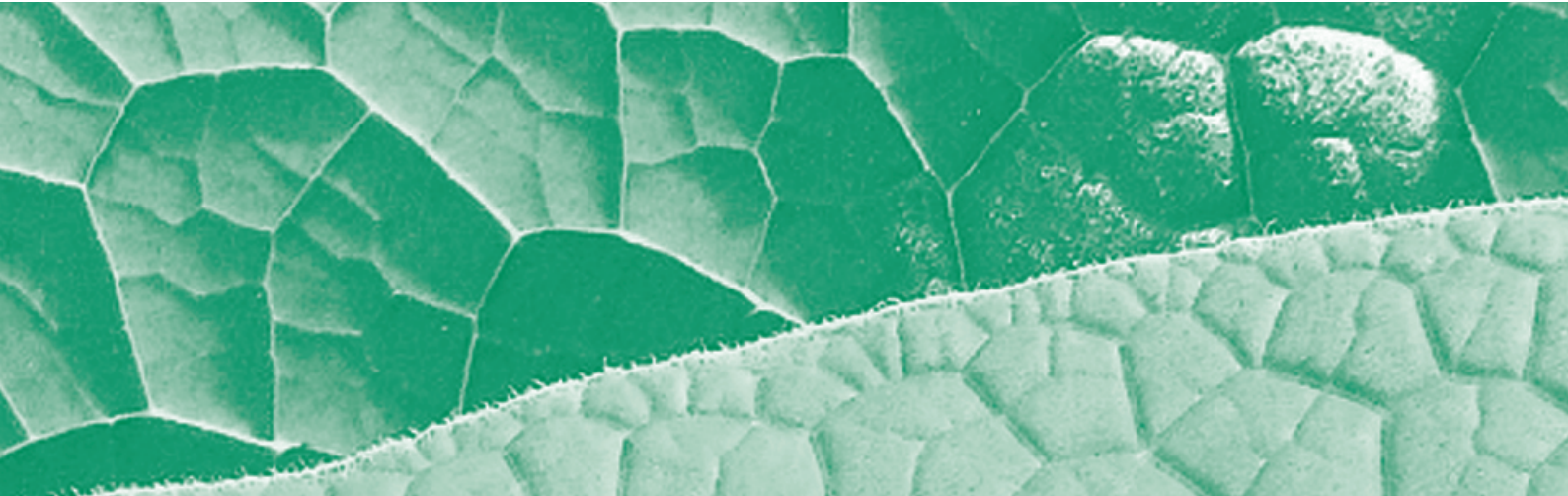


# Phytonews

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## Comfrey Ointment for Back Pain

Comfrey (*Symphytum officinale* and *Symphytum uplandicum*) is a highly popular herbal treatment amongst western medical herbalists for the topical treatment of bruises and sprains.

Despite anecdotal reports of its effectiveness and anti-inflammatory and analgesic properties<sup>(1,2)</sup> however, clinical trial validation of efficacy was lacking until relatively recently.

Since 2004 this situation has changed markedly, due to publication of results of three separate clinical trials involving an ointment made using comfrey root, conducted by German researchers.

The first trial involved application of comfrey ointment or a placebo ointment following acute unilateral ankle distortions (sprains), in a group of 142 patients<sup>(4)</sup>. Application of comfrey or placebo ointment commenced within 6 hours following the ankle sprain and continued over a period of eight days. Comfrey ointment application resulted in a

more rapid reduction in swelling and pain upon movement, as well as improved joint mobility.

The same researchers then undertook a second trial, also involving patients with acute ankle sprains that had occurred within the previous 6 hours, but this time using diclofenac gel as a control<sup>(5)</sup>. A total of 160 patients applied either comfrey or diclofenac four times daily over a 7 day period, and were examined on days 0, 4 and 7, using a range of measurements to assess ankle swelling, pain, ease of movement, and pain upon application of pressure.

While the tenderness reaction was reduced markedly by both comfrey ointment and diclofenac gel, those treated with comfrey experienced less pain upon pressure. After 7 days, 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%

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## Comfrey Ointment for Back Pain - *Continued*

in the comfrey group, compared to 70.8% in the diclofenac group. Both physician and patient assessments of these differences reached statistical significance.

Most recently, results from a third clinical trial involving comfrey ointment, this time for the treatment of acute upper or lower back pain, have been published in the *British Journal of Sports Medicine* <sup>(6)</sup>.

This latest trial was performed at the German Sport University in Cologne and three additional ambulatory centres for orthopaedics and sports medicine. A group of 120 patients with a mean age of 37 years, were treated with either an application of 4g comfrey ointment or a placebo ointment of similar appearance, three times daily for a period of 4-6 days. Patients were seen for evaluation of treatment effects on days 1 (two visits), 3 and 5, with the primary outcome measurement being the area under the curve (AUC) of the Visual Analogue Scale (VAS) on active standardised movement values. Secondary efficacy criteria were back pain at rest using assessment by patient, pressure algometry (a pain-time curve AUC over 5 days), global assessment of efficacy by the patient and investigator, analgesic medication consumption, and the level of functional impairment.

During the trial patients who received comfrey ointment treatment experienced a 95.2% drop in pain intensity on active standardised movement (from 104.8 to 12.7 mm (mean VAS sum), compared to a 37.8% drop in the placebo group (100.0 to 56.5 mm). This fall in pain intensity was already apparent at the second visit which took place one hour after ointment application, as shown by a 33% drop in pain intensity in the comfrey group versus 12% in the placebo group.

Using the primary variable alone, a superior effect of comfrey ointment to placebo for treatment of acute upper and low back pain independent of the pain localisation was shown, with a high level of statistical significance ( $p < 0.0001$ ). Furthermore, the lesser mean AUC's were found in all treatment centres involved in the study, although efficacy appeared to be less marked in those patients with milder rather than acute back pain.

Improvement was also measured in most of the secondary variables, with both the AUC of the reported back pain at rest, the AUC of the pressure

algometry in the trigger point as well as the global assessment of efficacy by the patients and the investigators showing significant superiority of the comfrey ointment group. Investigator ratings were an excellent or good assessment for 80% of patients in the comfrey treated group, versus 18.4% of patients in the placebo group. Patient global assessments were similar, being an excellent or good response in 78.4% of comfrey treated patients, versus only 18.4% in those who received placebo ointment. No difference in the frequency of adverse effects was reported between the comfrey and placebo groups.

**The authors concluded that comfrey ointment shows a remarkably potent and clinically relevant effect in reducing acute back pain, and that this reduction in pain was rapid and correlated to a parallel reduction in impaired movement.**

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## Echinacea Prevents Prostatic Hypertrophy?

Echinacea is best known for its immunostimulant and immunomodulatory properties, and most studies have evaluated its effects as a prophylactic or treatment for influenza and upper respiratory tract infections<sup>(1)</sup>. Application as an anti-inflammatory agent, however, also features prominently in its traditional use, including to treat snake bites and major abscesses<sup>(2)</sup>. Several anti-inflammatory actions have been confirmed by several pharmacological studies<sup>(3-9)</sup>.

While hormonal factors contribute, chronic inflammation is a major factor in disease progression of benign prostatic hyperplasia (BPH) in men. Almost all BPH specimens show inflammatory infiltrates at histologic examination, and an autoimmune

component to chronic inflammation is suggested <sup>(10)</sup>.

Based on this inflammatory component of BPH, and suspected anti-androgenic effects of Echinacea <sup>(11,12)</sup>, a team of researchers from Kaunas University in Lithuania, have investigated the effect of *Echinacea purpurea* root extract, on experimental BPH in rats<sup>(13)</sup>.

A '1 in 1' strength extract of Echinacea root was used in a rat model of BPH. This was induced in male rats by castrating them then injecting oestradiol and testosterone every two weeks, according to the method of Robinette<sup>(14)</sup>. Five different treatment groups were used: a control group of animals with intact prostate glands, animals after castration, animals with induced BPH, animals administered Echinacea extract for 4 weeks, and another group administered Echinacea for 8 weeks. The dose of Echinacea extract used was 50mg/kg, equivalent to a human dose of around 7-10grams dried *Echinacea purpurea* root daily.

At the end of the 4 or 8 week treatment period, animals were sacrificed and the prostate glands fixed in formaldehyde, then measured and examined histologically and by ultrasound.

Following Echinacea administration to the rats with hyperplasia, a significant reduction in prostate mass was observed, as well as a partial reversal of the degenerative changes in the prostate gland structure. Prostate size reduction was more pronounced in rats treated for 8 rather than 4 weeks ( $p < 0.001$  vs  $p < 0.03$  respectively), as was histological evidence of reduced inflammation.

Several positive effects were observed on the development of degenerative changes in the prostate structure following Echinacea administration. These included less atrophy of the glandular epithelium, less intracellular vacuoles, and the appearance of fragments of degenerating cells in the lumen of glands.

The same team of physiologists have previously published results of a similar study in the Lithuanian journal *Medicina*, in 2003<sup>(11)</sup>. This also reported a decrease in the weight of rat prostate glands, following four or eight weeks Echinacea administration.



**These studies using rats suggest that regular *Echinacea purpurea* root administration may have a preventative effect on the development of BPH, and that clinical studies in humans are warranted.**

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## Echinacea Promotes Wound Healing

Another use of Echinacea in both a traditional North American as well as modern phytotherapeutic context, is to assist with wound healing. Historically *Echinacea angustifolia*, *Echinacea pallida*, and *Echinacea purpurea*, were all used as wound healers, both topically and through oral administration<sup>(1)</sup>.

This alleged benefit has been little explored, apart from a study in pigs which reported favourable effects on vocal fold wound healing as well as anti-hyaluronidase activity, following topical Echinacea application<sup>(2)</sup>. Anti-inflammatory, anti-hyaluronidase and wound healing activities have also been reported in rats for the *Echinacea pallida* constituent echinacoside<sup>(3)</sup>, although this has poor oral bioavailability<sup>(4)</sup>.

Researchers based at Iowa State University recently investigated the effects of *Echinacea pallida* on the rate of healing of skin wounds in mice during a period of chronic stress<sup>(5)</sup>.

Chronic stress is known to have an immunosuppressive effect thought to be related largely to increased levels of glucocorticoid hormones, and is associated with impaired wound healing<sup>(6-8)</sup>.

An ethanol extract of dried *Echinacea pallida* root or control vehicle was given to mice exposed to repeated restraint stress and non-restrained controls, according to the method of Padgett et al<sup>(6)</sup>, for a period of seven days. Restraint stress and Echinacea administration occurred for three days prior to and four days post skin wounding, and wounds were photographed immediately after wounding then daily until the end of the experiment. Wound area was measured, and healing was assessed beginning seven days after wounding took place.

A further study was also undertaken which involved administration of the Echinacea extract as well as plasma corticosterone measurements and recording of the body and spleen weights in restraint stressed mice.

Echinacea was shown to accelerate wound closure in the stressed mice, but had no apparent wound healing effect for the non-stressed mice when compared to their respective controls.

In the second set of experiments, measurements of plasma corticosterone levels found that Echinacea did not modulate these, but that it could improve wound healing when plasma corticosterone levels were high. This suggests that the improved wound healing of Echinacea in stressed mice is not modulated through glucocorticoid hormone signalling, but occurs through other mechanisms.

**While not a human study, this supports a possible role for Echinacea root to help optimise immunity and to enhance wound healing during stress. These benefits would seem likely to extend also to encouraging post-surgical recovery, surgery itself being an intrinsically stressful event.**

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## Withania Useful in Parkinsons Disease?

*Withania somnifera* (Ashwagandha) is a popular Indian herbal medicine, the root of which has been used for more than 4000 years in Indian ayurvedic medicine. It is used to treat a wide range of conditions including stress, anxiety, insomnia, arthritis and neurodegeneration<sup>(1-4)</sup>. Pharmacological studies to date have found evidence of anti-inflammatory, antitumour, antistress, antioxidant, immunomodulatory, hepatoprotective and hypocholesterolaemic activities<sup>(5-13)</sup>.

Age-related disorders and mobility difficulties have been treated with *Withania*<sup>(2,14)</sup>, which is sometimes known as "Indian ginseng" outside of India. Japanese researchers have also found that an extract of *Withania* and several withanolide constituents can induce axon and dendrite outgrowth in rat neurons and human neuroblastoma cell lines, suggesting potentially beneficial effects on neuronal regeneration<sup>(15-17)</sup>.

Chronic administration of *Withania* has neuroprotective effects, particularly during periods of stress<sup>(18,19)</sup>. Favourable effects have been reported in an animal model of tardive dyskinesia<sup>(20)</sup>, and reversal of haloperidol induced catalepsy<sup>(21)</sup>. These conditions are relatively common adverse effects of long term neuroleptic drug treatment, and have a similar pathophysiology to that of Parkinson's disease.

Parkinson's disease (PD) is a neurodegenerative disorder characterised by loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in tremor or trembling in the hands, arms, legs, jaw and face; rigidity or stiffness of the limbs and trunk; bradykinesia or slowness of movement, and postural instability or impaired balance and coordination.

Apart from abnormalities in dopamine neurotransmission, recent studies suggest that oxidative stress is involved in both the initiation and progression of PD<sup>(22,23)</sup>. Several indices of oxidative and nitrosative stress are increased in PD patients, and free radicals can induce lipid peroxidation and DNA damage, leading to neuronal death. Depletion of glutathione is also an early biochemical change seen in the brains of PD patients<sup>(24)</sup>, as well as increased brain levels of thiobarbituric acid reactive substance (TBARS), a marker of lipid peroxidation<sup>(25,26)</sup>.

A team of Indian researchers have recently examined the effect of

*Withania* on a mouse model of Parkinsons disease<sup>(27)</sup>. Three groups of mice were used, one an untreated normal control, one an untreated Parkinson's disease control injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce Parkinsonian like abnormalities, and the other which as well as MPTP injection received an oral dose of 100mg/kg of *Withania somnifera* for 7 days.

After 8 days behavioural studies were performed to measure motor function skills (a horizontal grid hang test, and a rotarod test), following which the animals were sacrificed, then their striatum removed and subject to various biochemical analyses. These included measurements of dopamine and its metabolites 3,4-dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA), as well as glutathione (GSH), glutathione peroxidase (GPx), and TBARS as a lipid peroxidation marker.

As expected, MPTP injection lead to an elevation in brain levels of TBARS, and reduced levels of dopamine, DOPAC, HVA, GSH and GPx, and induced TBARS levels, compared to the control group. Motor skill deficiencies were also seen in these PD mice as determined by the hang and rotarod tests.

Oral treatment of PD mice with *Withania* for 7 or 28 days increased dopamine, DOPAC and HVA levels and normalised TBARS levels in the corpus striatum. *Withania* treated mice also showed improved motor function, and striatum levels of GSH and GPx were increased after 28 days of *Withania* treatment. The authors concluded that their data suggests *Withania* is a potential drug to treat the catecholamine, oxidative damage and physiological abnormalities seen in the PD mouse.

This was a continuation of earlier work by the same team of workers, who previously reported a similar improvement in the behaviour and antioxidant status of PD mice, along with a reduction in the level of lipid peroxidation, following oral *Withania* root treatment<sup>(18)</sup>. They have also recently documented similarly beneficial effects in a mouse model of PD for an extract made using the leaf rather than root of *Withania*<sup>(28)</sup>.

Another group of researchers have also recently published results of a study involving *Withania* in a rat model of Huntington's disease. In these experiments, improvement in behavioural and biochemical alterations took place following 14 days administration of large doses of *Withania* root extract<sup>(29)</sup>.

**Collectively, these studies implicate a potentially useful contribution that *Withania somnifera* root extract could make to the treatment of Parkinsons disease and Huntington's disease, although further studies involving humans are required.**

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## Ginkgo and Chamomile for ADHD?

Attention-deficit hyperactivity disorder (ADHD) is a condition characterised by developmentally inappropriate inattention and impulsivity, with or without hyperactivity<sup>(1)</sup>. In adolescence and adulthood, those with ADHD are at risk for learning disabilities, psychological disorders, substance abuse and addictions, and aggressive conduct disorder<sup>(2,3)</sup>.

Prevalence rates vary from country to country, but rates of diagnosis at least, seem to be rising in industrialised countries. In the US approximately 10% of boys and 4% of girls have been diagnosed with ADHD, and adult prevalence rates are around 70% of those in children. In 1996 at least 40% of children referred to outpatient child psychiatry clinics in the US were diagnosed with ADHD, and by 2003, approximately 2.5 million young Americans were being treated with medication for ADHD symptoms.

Stimulants such as methylphenidate (Ritalin®) and amphetamines are the most widely used medications approved for ADHD in children and adolescents<sup>(4)</sup>. While these are generally efficacious, adverse effects include decreased appetite, insomnia and a potential for abuse, and some concerns exist around long term health effects<sup>(5,6)</sup>.

A researcher based at the Child and Adolescent Psychiatry unit, Regional Hospital Bozen, in Bolzano, Italy, has recently reported separately his observations on the use of two well known herbs, Chamomile and Ginkgo, in teenagers with ADHD<sup>(7,8)</sup>. These two herbs, as well as Hops, Valerian, Passionflower and Lemon Balm, have previously been reported to have some possible benefit in treating ADHD<sup>(9)</sup>.

In the Ginkgo study, six subjects aged 17-19 years (four male, two female), were given a dose of standardised Ginkgo extract at a dose of 200mg for 4 weeks. No other medication was taken, and subjects were evaluated after one month using ratings of ADHD spectrum behaviours and assigned ADHD factor scores<sup>(8)</sup>.

After Ginkgo treatment, patients reported a drop in the mean ADHD score. Predominant behavioural effects were a calming effect, reduced anxiety, and improved frustration tolerance. At the end of treatment, nearly all patients expressed a wish to continue treatment.

This is not the first trial involving a Ginkgo containing preparation for

ADHD. In 2001, a team of Canadian researchers reported results of a pilot open study using a combination of Ginkgo and American Ginseng (*Panax quinquefolium*) in ADHD patients<sup>(10)</sup>. A capsule containing a mixture of standardised extracts of American Ginseng (200mg) and Ginkgo (50mg) was used, although the extract strengths and therefore quantification of the original herb dose was not specified. Thirty six participants aged between 3 and 17 years took the herbal capsules twice daily for 4 weeks. Of these, 25 were taking other medications concomitantly, mostly Ritalin®.

Some improvement in symptoms was reported after 2 weeks of treatment, with an even greater improvement occurring after 4 weeks. Improvement was measured in all attributes examined, and in each of the three areas that are most troublesome in ADHD (hyperactivity, cognitive problems and oppositional behaviour) at least 50% of the subjects responded favourably after 4 weeks treatment.

This was a small and uncontrolled study, which along with the subjective nature of the parenteral assessment methods used, has limitations in its design. Nevertheless, it suggests potential benefits of a Ginkgo-Ginseng combination in the doses given, in children and adolescents with ADHD.

Preliminary observations of the outcomes following Ginkgo use by three young men with autism have also been recently reported by the same author. During the 4 week treatment period a modest improvement was reported in caregiver but not clinician ratings, particularly with symptoms of irritability, hyperactivity, inadequate eye contact and inappropriate speech<sup>(11)</sup>.

The Chamomile study was a crossover study, involving two male ADHD patients aged 14 and 16 years old who took Chamomile tablets or placebo three times daily for 4 weeks<sup>(7)</sup>. Again, results from the ADHD Rating Scale<sup>(12)</sup>, suggested a slight improvement in symptom scores during Chamomile as opposed to placebo treatment. Anxiolytic activity by the flavonoid apigenin, shown to interact with central benzodiazepine receptors or their enzymes, may be contributory to such benefits of Chamomile in ADHD<sup>(13-16)</sup>.

Another preliminary open trial involving administration of St Johns Wort to three male patients



with autistic disorder, who had not tolerated or responded to drug therapy (methylphenidate, clonidine or desipramine), failed to find significant evidence of benefit<sup>(17)</sup>. A subsequent open trial with ten subjects who took St Johns Wort for 6 weeks, however, did produce a modest symptom improvement<sup>(17)</sup>.

**These very small preliminary studies and observational reports collectively suggest a potential role for Ginkgo and possibly Chamomile as single or adjunctive treatment for patients with ADHD. However further placebo-controlled and randomised trials involving larger patient numbers are required to confirm any such benefits.**

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## Anti-Cancer Properties of *Panax notoginseng*

Korean Ginseng (*Panax ginseng*) and American Ginseng (*Panax quinquefolium*), are well known members of the Panax or Ginseng family, used primarily as general tonics and adaptogens in traditional Chinese and western herbal medicine<sup>(1)</sup>. The third member, however, Tienchi Ginseng or Sanchi (*Panax notoginseng*), is also popular in China, being used mostly for conditions associated with poor blood circulation including cardiovascular disease, inflammation, trauma, internal and external bleeding, and to improve memory<sup>(2)</sup>. A recent Cochrane Review concluded that it seems to be beneficial and safe for acute ischaemic stroke, although called for further well-designed clinical trials<sup>(3)</sup>.

Like its cousins, Tienchi Ginseng contains ginsenosides, a group of triterpenoid saponins known to contribute greatly to therapeutic effects and found nearly exclusively in Panax species. Up to 150 different ginsenosides have been characterised<sup>(4)</sup>, many of which are found in two or all three Panax species. Levels of ginsenosides Rb1, Re and Rd are generally higher in American Ginseng than they are in Korean Ginseng, while in Korean Ginseng, contents of the ginsenosides Rg1, Rb2 and Rc are generally higher than in its American cousin. It should be noted, however, that individual ginsenosides are metabolised or transformed to other ginsenosides by gastrointestinal tract bacteria or heating, drying and steaming respectively, therefore processing, as well as analytical methods used, are highly relevant<sup>(4,5)</sup>.

A recent review which discussed comparative differences between Korean and American Ginseng suggested that as a result of the higher content of Re in American Ginseng it is probably a stronger anticancer agent, while the higher contents of Rg1 in Korean Ginseng

probably impart it with more stimulant or energising properties<sup>(6)</sup>.

Tienchi Ginseng contains notoginsenoside R1, and ginsenosides Rg1, Rd, Rb1, Rc and Rd as its main saponins, most of which are found also in Korean or American Ginseng. Several common pharmacological effects such as neuroprotective and chemoprotective actions therefore seem likely due to ginsenoside content, although differences also exist. A comparative study published recently reported a significantly greater antiplatelet effect for steamed but not raw Tienchi Ginseng than for Korean or American Ginseng<sup>(7)</sup>.

Interestingly, quantitative comparisons of total major saponins between these three major Ginseng species have reported Tienchi Ginseng to contain the highest content of the twelve total saponins measured<sup>(8)</sup>. Tienchi Ginseng is also substantially cheaper than Korean and American Ginseng, and one author at least has suggested it as a cheaper substitute for American Ginseng with regard to antioxidant activity<sup>(9)</sup>.

An appraisal of the traditional use and ginsenoside content of Tienchi Ginseng points to potential anti-cancer properties also for this herb, in a similar manner to those of Korean and American Ginseng. Sensitisation to the cytotoxic effects of ionising radiation on sarcoma in mice has been reported following parenteral administration of Tienchi Ginseng or purified ginsenoside Rb1 obtained from it, without harmful effects on the bone marrow<sup>(10)</sup>. Serum obtained from dogs fed Tienchi Ginseng has also been found to exhibit apoptosis promoting effects against human precancerous gastric cells<sup>(11)</sup>.

Interest in the potential anti-cancer properties of this species seems to have increased further lately, with a number of studies into anti-cancer bioactives of Tienchi Ginseng extracts being published by American and Chinese researchers<sup>(12, 13, 14, 15)</sup>.



A dammarane-type triterpene saponin extract from the leaves of Tienchi Ginseng (20(S)-25-OCH<sub>3</sub>-OOD (PPD25)), was first shown to have cytotoxicity against a variety of cancer cells including prostate cancer in 2008<sup>(12)</sup>. The same product has recently been evaluated for anti-cancer properties using three colon cancer cell lines and one lung cancer cell line<sup>(14)</sup>. Significant inhibition of cell proliferation and induction of apoptosis was measured using all four cancer cell lines. These effects were related to reduced expression of the beta-catenin protein, which plays a critical role in carcinogenesis<sup>(16)</sup>. The authors of this study suggest that PPD25 might be useful as a chemotherapeutic and/or chemopreventive agent for colon and lung cancer.

This research team have also recently studied the in vitro effects of different plant parts of Tienchi Ginseng on human colorectal cancer cell<sup>(15)</sup>. While extracts from the root, rhizome, flower and berry all exhibited concentration-dependent antiproliferative effects, the strongest effects were produced by an extract made from the flowers.

Most recently, PPD25 has been reported to decrease survival, inhibit proliferation and induce apoptosis and G1 cell cycle arrest in three different human lung cancer cells<sup>(13)</sup>. It also inhibited the growth of A549 lung cancer xenograft tumours, demonstrated low toxicity to non-cancer cells, and had no observable toxicity when administered to animals. The authors concluded that further preclinical and clinical development of this Tienchi Ginseng saponin for lung cancer is warranted.

Potentially beneficial properties of this phytomedicine when used in conjunction with chemotherapy medication, have also been suggested. Enhancement of the anti-cancer effects of 5-fluorouracil and irinotecan on human colorectal cancer cells has been reported for a root extract of Tienchi Ginseng<sup>(17, 18)</sup>, while a flower extract has been reported to enhance the cytotoxicity of 5-fluorouracil on human colorectal cancer cells<sup>(17)</sup>. These effects thus appear similar to the potentiation of anticancer drug activities reported in vitro for both Korean and American Ginsengs<sup>(19,20, 21)</sup>.

**Further investigations into the anti-cancer properties of Tienchi Ginseng, and its possible use as adjunctive therapy during radiotherapy or chemotherapy treatment, are justified.**

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## Wild Strawberry Leaves Improve Cardiac Function

The sensory and visual properties of strawberries have been the subject of a great deal of breeding over many years. The Wild or Woodland Strawberry (*Fragaria vesca*), from which the modern garden strawberry (*Fragaria x ananassa*) is derived, is nowadays a less well known plant with much smaller fruits, but grows readily as a wild plant in many countries including New Zealand.

As with many other berries, potent antioxidant activity is found within the flesh of strawberries, attributable to their rich content of polyphenolic compounds and phenolic acids<sup>(1,2,3)</sup>. Interestingly, this antioxidant activity has been reported to be especially

prominent in wild rather than cultivated varieties<sup>(4,5)</sup>.

Potential health benefits of strawberries relate to this phytochemistry, and dietary consumption may lower the risk of several chronic diseases<sup>(4,2)</sup>. This includes protection against various forms of cancer<sup>(6)</sup>, age-related oxidative stress, inflammatory responses, diverse degenerative diseases, bacterial infections<sup>(7,2)</sup>, and improvement in ocular health. Antioxidants are also known to help lower the risk of cardiovascular events by inhibition of LDL-cholesterol oxidation, promotion of plaque stability, improved vascular endothelial function, and decreased tendency for thrombosis.

While the fruits are the part of the strawberry plant normally considered of interest, both the leaves and fruit of wild strawberries were once used for food particularly during times of scarcity<sup>(8)</sup>. Preparations of the leaves were also used traditionally to treat diarrhoea, as a mouthwash for oral mucosal inflammations, and for haematuria and urinary tract conditions, rheumatism, gout and arthritis<sup>(9)</sup>.

Like the fruit, strawberry leaves are rich in phenolic compounds with antioxidant potential. These include anthocyanidins, flavonoids, condensed as well as ellagic tannins, and several novel phenylethanoid derivatives of phenylpropanoid glycosides<sup>(10)</sup>. Wild strawberry leaves were once identified as a useful experimental material for studying the physiology of flavonoids and procyanidins<sup>(11)</sup>, and young leaves apparently contain a higher total phenolic content than the fruit or old leaves<sup>(12)</sup>. In a recent study involving 70 different plant extracts, an extract of wild strawberry leaves was shown to have one of the highest levels of total phenolics and related antioxidant capacity<sup>(13)</sup>.

Based on the above, a team of researchers in Croatia recently evaluated the effects of an aqueous extract of wild strawberry leaves on various cardiovascular parameters, using Hawthorn (*Crataegus oxyacantha*) extract as a control. These included effects on heart contractility, coronary flow, oxygen consumption and electrophysiological function of isolated guinea pig heart, and isolated intact and endothelium-denuded rat aortic rings.

Both extracts induced similar dose-dependent vasodilation using isolated aortic rings from rats. Endothelium-denuded and intact rings exposed to nitric oxide synthase inhibitor I-NAME or the cyclooxygenase inhibitor

indomethacin, were used to explore mechanisms of these vasodilatory effects. Removal of the endothelium prevented the vasodilatory response, while L-NAME or indomethacin exposure strongly diminished it. These results suggest that the vasodilatory activity of strawberry leaf is endothelium-dependent, and is likely to be mediated by nitric oxide and cyclooxygenase products.

The fact that the vasodilatory effect of Wild Strawberry leaves was similar to that of Hawthorn extract is of great interest. In European herbal medicine Hawthorn is the most studied and promising agent in cardiovascular system indications. Beneficial effects seem likely in a range of cardiovascular conditions including heart failure, mild hypertension, coronary artery disease and angina<sup>(14,15)</sup>.

No significant effects were produced by Strawberry leaf extract on the heart rate and contractility of isolated guinea pig hearts, main parameters of cardiac action that determine oxygen demand. Nonetheless, coronary flow increased with simultaneous decrease of oxygen extraction by the heart. This disproportionate increase in oxygen delivery relative to oxygen demand

suggests potential benefits in coronary artery disease and angina.

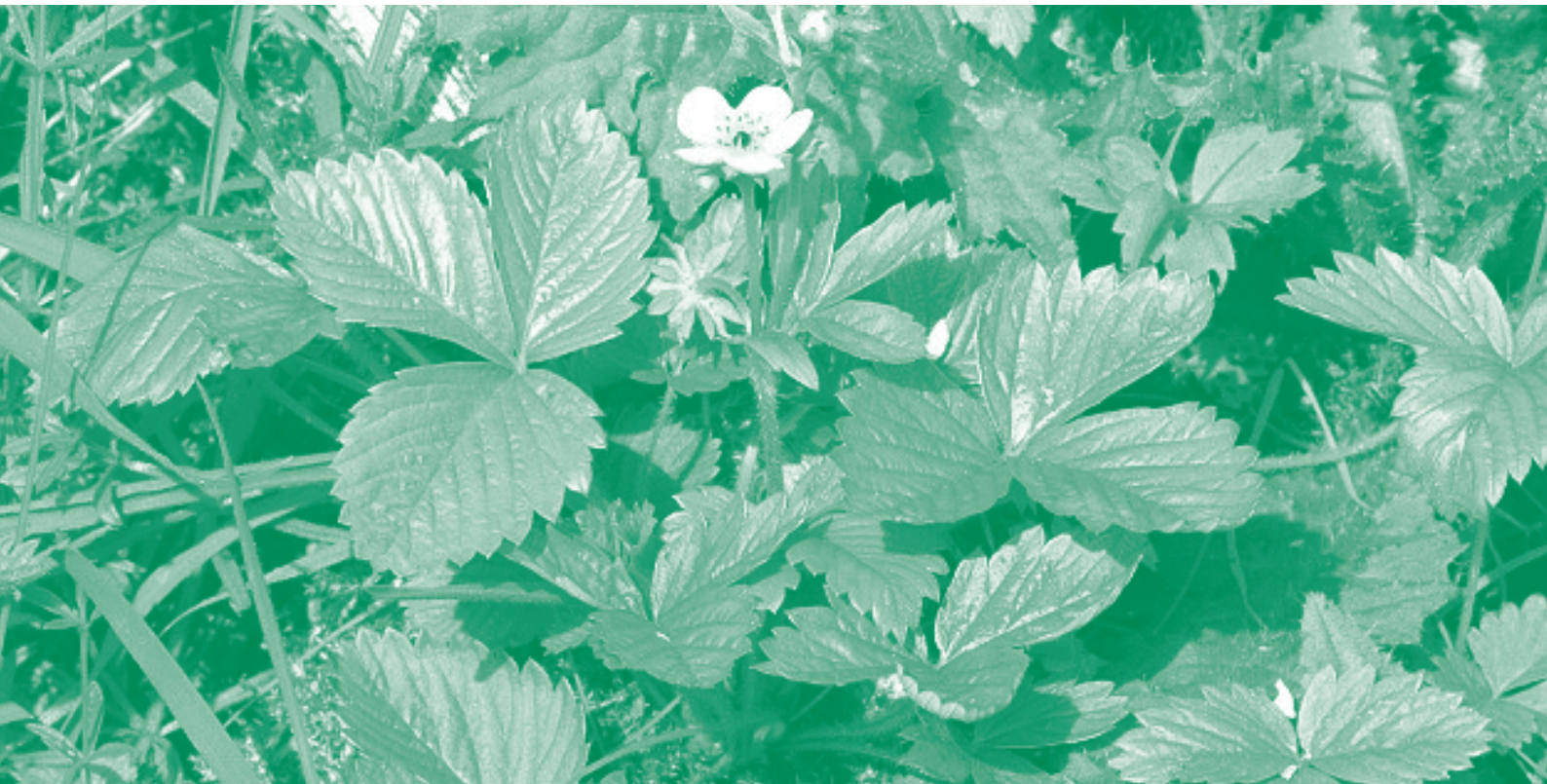
Both Strawberry and Hawthorn extracts were analysed phytochemically, and flavonoid and non-flavonoid constituents confirmed. When the related antioxidant capacity for each extract was measured, that for strawberry was found to be more than 50% stronger than Hawthorn.

Potentially protective effects against cardiovascular diseases by strawberries are being revealed from in vitro and animal studies<sup>(4,16,17,18)</sup>. Anti-thrombotic effects have been reported for the fruit<sup>(16)</sup>, and while a study involving 26,966 women failed to find any connection between strawberry intake and the risk of incident cardiovascular disease or hyperlipidaemia, a higher intake was linked with producing a slight lowering in the risk of having elevated C-reactive protein levels<sup>(18)</sup>.

**What this latest study suggests is that the leaves of this popular plant may also hold similar value. Furthermore, the more obscure wild form of the strawberry plant from which modern fruits have evolved, could show particular promise as a useful herb for cardiovascular health in humans.**

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