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St John's Wort

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Antidepressant Effects of St John's Wort Last Longer than those of Citalopram?

The efficacy of St John's Wort *(Hypericum perforatum)* as an antidepressant medication is well established, and various Hypericum products have been shown to exhibit similar activity to that of antidepressant drugs.

A Cochrane Database review published in 2008 which appraised 29 trials including 17 where comparisons were made with antidepressant drugs, found the results of these to be statistically homogeneous[1].

This, and other reviews of Hypericum clinical trials, concluded that not only is Hypericum non-inferior to antidepressant drugs in terms of exhibiting antidepressant activity, but it is additionally much less likely to be associated with adverse effects[2-5].

As nearly 50% of patients diagnosed with major depression will encounter at least one or more depressive episode[6-8], prevention of relapse and recurrence is an important component in its successful treatment[9-14].

While antidepressant treatment invariably starts during the acute phase of the illness and normally leads to remission from depressive symptoms within 6-8 weeks, ongoing treatment for several months should generally take place to help prevent a relapse.

In this context, evidence of a potential advantage of Hypericum over antidepressant drugs has emerged recently through re-analysis of the data from two clinical trials involving different Hypericum extracts[15,16].

In the first of these, an Austrian team re-evaluated the data from two placebo controlled clinical trials, to re-analyse a subset of patients suffering from an acute episode of mild depression[15]. This included a total of 217 out of the more than 1,200 patients involved, with pre-treatment scores of 20 or less on the Hamilton Rating Scale for Depression (HAMD).

At the end of the 6 week treatment period, the response rate (i.e. patients with a HAMD total score decrease of at least 50%) ranged from 64% to 73% for different Hypericum dosage groups used, but was only 36% for placebo. A substantial increase in the probability of subsequent remission (HAMD total score less than or equal to 7 points), was also associated with Hypericum treatment in this trial.

Results from a large multicentre, double-blind, randomised trial involving 426 patients in Germany and Sweden who took Hypericum or placebo for 6-12 months, are also of interest[17]. This found that continuous Hypericum treatment was associated with a 18.1% rate of relapse, versus a relapse rate of 25.7% for those who received placebo.

Most recently, potential differences between Hypericum and other antidepressant drugs in terms of the duration of response following treatment have been evaluated by a team of German researchers[16]. An initial six week clinical trial involving 394 outpatients diagnosed with mild to moderate depression (HAMD score ≥20-24) took place between October 2002 and May 2003. This showed the efficacy of Hypericum to be similar to that of citalopram 20mg and superior to that of placebo, with a total of 188 patients being classified as responders at the end of the trial (HAMD score of ≤ 10)[18].

Of these 188 responders, 154 were re-evaluated at one, two and three years following the initial treatment, to determine the duration of response and possible occurrence of a relapse and/or recurrence[16]. Relapse was defined as the reappearance of symptoms within six months after the end of the clinical trial, and recurrence as the appearance of symptoms in a new episode more than six months after the end of the clinical trial. Data was collected retrospectively between February and April 2008, from 16 out of the initial 20 study centres.

Of the 154 patients, 30 (19.5%) relapsed within the first half year after end of treatment. The relapse rate was highest in the group of patients who had responded to citalopram (14 patients, or 25.9%), and lowest in the Hypericum group (8 patients, or 14.8%). Rates for relapse and recurrence combined were also lowest in the Hypericum group at one, two and three years after the end of treatment.

These differences between Hypericum and citalopram fell short of statistical significance ($p = 0.0882$), although a pair-wise comparison of Hypericum against placebo was highly significant ($p=0.0288$). The median time to occurrence of a relapse and/or recurrence was 802 days for the placebo group, 1755 days for the citalopram group and 1817 days for the group of Hypericum responders. No differences in the intensity of relapse was recorded between the three groups.

While further research into this subject using larger patient numbers and more in depth analysis is called for, this latest study suggests another possible advantage of Hypericum over antidepressant drugs in the treatment of depressive illness.

Hypericum's reputation has suffered from adverse press during recent years due to the risk of interactions with some pharmaceutical drugs[19-20]. However, provided it is prescribed by suitably qualified health professionals, and evaluation of potential drug interactions takes place, this latest study further supports the use of Hypericum as a first line choice of antidepressant medication.

The potential economic benefits through use of Hypericum rather than antidepressant drugs, were discussed in a recent issue of the *Australian and New Zealand Journal of Psychiatry*[21]. Given that a clear advantage over antidepressant drugs has been demonstrated through similar rates of efficacy, lower risk of adverse effects and good compliance, the authors suggest that the comparatively low cost of Hypericum relative to newer generation antidepressant drugs makes it worthy of consideration in the economic evaluation of treatments for mild to moderate depression.

As the indirect costs of depression are more than five times greater than the direct treatment costs, the better compliance with Hypericum treatment and its potential ability to produce a more long lasting response, adds to the already persuasive case for it to be used as a first line treatment option in depression.

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St John's Wort

Withania

Withania Improves Sperm Quality

Male infertility is estimated to contribute to around 50% of cases of infertile couples, yet few specific treatments are available, due to the unexplained and heterogeneous nature of the disorders[1]. This lack of available specific therapies has catalysed the search for general therapies that may achieve good outcomes, at least in a subcategory of patients. Some forms of male infertility seem to be caused by oxidative stress and hormonal imbalance, and mounting evidence suggests that seminal oxidative stress is involved in many cases of idiopathic male factor infertility [2].

Seminal plasma and spermatozoa contain a range of antioxidant mechanisms to counteract the toxic effects of reactive oxygen species (ROS). These include several antioxidant enzymes, and high concentration of thiol groups, ascorbic acid and uric acid[3]. While ROS production is essential for sperm capacitation, acrosome reaction and oocyte fusion[4], uncontrolled and excessive production of ROS may cause oxidative stress, peroxidative injury to the sperm membrane and consequent impairment in sperm motility and morphology[2,5]. Oxidative stress, along with derangement in hormone levels, are negatively correlated with sperm concentration and motility in infertile men[6].

Withania somnifera (Ashwaghanda) is a popular medicinal herb in India, reported to possess adaptogenic, anti-stress, anxiolytic, anti-Parkinsons and geriatric tonic properties[7,8]. Withania also has a folklore reputation as an aphrodisiac, and inhibits lipid peroxidation in animals under stress[9]. Studies in rats have reported improvement in folliculogenesis in females, epididymal sperm pattern in adult males[10] , and in testicular development and spermatogenesis in immature rats[11].

Encouraged by the above animal studies, a team of Indian researchers have recently investigated the effect of a three month treatment with Withania on semen quality in infertile and fertile men[12,13].

A control group of 75 normal healthy and fertile men and 75 infertile men were recruited from a urology outpatient department. The control (fertile) group comprised age-matched men with evidence of recent paternity or recent initiation of pregnancy, and exhibiting a normal semen profile. Three groups each of 25 men participated in the infertile men category, one with normal semen profile but infertility of unknown aetiology (normozoospermic), one with a low sperm count but normal motility and morphology (oligozoospermic), and the last with normal sperm count and morphology but low motility (asthenozoospermic).

Subjects with diabetes, hypertension, arthritis, tuberculosis, HIV, on drugs, or with other conditions known to influence oxidative stress, were excluded. Complete physical, biochemical and semen examinations were performed, and infertile cases where a contribution from the female partner was likely were excluded. Dietary patterns were also monitored on a monthly basis during the trial.

Each subject was prescribed 5 grams per day of Withania root powder to be taken orally with milk for the three month period. Semen was collected for analysis pre- and post-Withania treatment, from both the fertile and infertile groups of men.

Following Withania treatment, sperm concentration increased and motility improved significantly in all three subgroups of infertile men, although the motility increase in asthenozoospermic infertile men was less than optimal. Semen volume also increased significantly in normozoospermic and oligozoospermic, but not asthenozoospermic men.

Improvement in oxidative biomarkers was also measured following Withania treatment. Lipid peroxides and protein carbonyl groups were elevated in the seminal plasma of all infertile groups, but after treatment underwent a significant decline. Infertile men also had lower levels of superoxide dismutase (SOD) activity and glutathione in seminal plasma than fertile men, but Withania treatment reversed both these indicators of oxidative activity.

These antioxidant properties of Withania were shown to be better than those previously determined in *Mucuna pruriens*, another herb shown to improve male infertility[15,16].

Withania treatment was also associated with an increase in suboptimal levels of serum testosterone and serum luteinising hormone in all groups of infertile men. Elevated levels of follicle stimulating hormone and prolactin in the serum of oligozoospermic and asthenozoospermic men compared with fertile men, were also reduced by Withania treatment.

In a separate study on the same cohort, the researchers produced results from measurements on apoptosis (normal cell death) and intracellular reactive oxygen species (ROS) concentration of spermatozoa, as well as essential metal ions in seminal plasma from the infertile men. The latter seem to be involved in male infertility[12,13,14], with copper, zinc and iron being cofactors for the antioxidant enzymes SOD and catalase.

Prior to Withania treatment, sperm apoptosis and intracellular ROS concentrations were significantly higher, and concentrations of the essential metal ions copper, zinc, iron and gold were lower in all groups of infertile compared to fertile men[13]. Withania treatment significantly reduced apoptosis in normozoospermic and oligozoospermic men and ROS concentrations in oligozoospermic and asthenozoospermic men. It also increased the relatively low levels of all four metal ions measured pre-treatment in normospermic men, copper, zinc and gold in oligozospermic men, and zinc, iron and gold in asthenozoospermic infertile men. Metal ion levels in infertile men post Withania treatment were in fact comparable to those measured in the fertile men.

These studies provide convincing evidence, that consuming the equivalent of 5 grams dried Withania root powder per day, over a three month period, can have a number of benefits on semen quality and fertility in men. Further studies involving larger numbers of participants are now needed.

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Black Cohosh in Patients on Tamoxifen

Early or sudden menopause is a frequent consequence of anti-cancer drug therapy in breast cancer patients, yet hormone replacement therapy is not recommended due to the risk of hormone-induced tumour progression [1]. Alternative therapies to help alleviate menopausal symptoms in breast cancer patients are therefore often sought.

Roots and rhizomes of the North American native plant Black Cohosh *(Cimicifuga racemosa)* are one of the most popular ingredients of natural health products promoted for menopause. Unlike hormone drug therapy, Black Cohosh seems to act as a modulator rather than agonist or antagonist of oestrogen receptors[2,3]. Black Cohosh's safety in patients with breast cancer is nevertheless a subject of intense interest.

A 2003 review on the safety of Black Cohosh for the treatment of menopause symptoms, which evaluated all published literature and the FDA and WHO adverse-event reporting systems, found a 5.4% incidence of adverse events, 97% of which were minor and did not result in discontinuation of treatment. The author concluded that specific Black Cohosh extracts are a safe alternative for women in whom oestrogen therapy is contraindicated[4] .

Inhibition of human breast cancer cell proliferation by Black Cohosh extracts has been reported from several in vitro studies using both oestrogen receptor-positive and oestrogen receptor-negative cell lines [5-11]. In vitro potentiation of the anti-cancer effects of tamoxifen[12] and doxorubicin[13] has also been reported.

Two retrospective human studies by German and American researchers have examined the risk of breast cancer or breast cancer recurrence in women who had taken Black Cohosh. Findings from these studies, which involved nearly 2000 women, suggest possible cancer preventative benefits through regular use of this phytomedicine [14-16].

Two small clinical trials to date have evaluated combined administration of Black Cohosh with tamoxifen, or Black Cohosh alone, in women who had survived breast cancer[17-18].

No safety concerns were identified, although relief of menopausal symptoms was only measured in the trial where combined tamoxifen and Black Cohosh treatment took place over a 12 month period.

Findings from a recent prospective observational study in 50 breast cancer patients have provided further evidence of the safety and apparent efficacy of Black Cohosh in women on tamoxifen[19].

The study followed participants in a German inpatient rehabilitation programme following primary breast cancer treatment. All patients received a daily dose of 20 to 80mg of an isopropranolic extract of Black Cohosh, alongside tamoxifen at doses ranging from 10 to 40mg per day. A questionnaire to assess menopausal symptomatology was completed prior to Black Cohosh treatment, then after 1,3 and 6 months of treatment. A total of 35 patients took treatment for a six month period.

Black Cohosh treatment was associated with improvement in hot flushes, sweating and sleep problems, as well as vegetative somatic complaints, but not urogenital complaints. Nearly all adverse effects were attributed to tamoxifen therapy, and no tumour recurrence was reported during the observation period.

The results from this study would seem to provide further reassurance of the safety of low dosages of Black Cohosh when taken by women with a history of breast cancer. Various shortcomings of this study should be considered however, such as the lack of a placebo control group, and the possible contribution of the previous intensive rehabilitation care programme to the beneficial outcomes reported.

Longer term studies involving greater patient numbers are still required to further explore the effects of combined Black Cohosh and tamoxifen administration.

References at end of next article

Black Cohosh

Black Cohosh Liver Toxicity Risk Over-Rated?

Concerns about possible hepatotoxicity of Black Cohosh first appeared following publication of two case reports in Australia in 2002[20]. Various other reports of liver damage attributed to Black Cohosh have since been made, mainly in Australia and the U.S.[21-23].

While regulatory bodies in several countries subsequently reacted by introducing a label warning requirement by manufacturers advising consumers that Black Cohosh may harm the liver, the ability of this phytomedicine to produce liver damage has been challenged by various authors [21-22].

Factors such as the possible adulteration of some brands not made under Good Manufacturing Practice with cheaper Asian species of *Cimicifuga;* a contribution from as yet uncharacterised viruses or other unknown causes of hepatitis; and the high level of global usage of Black Cohosh supplements, should be considered when appraising any possible hepatotoxicity[21].

A recent review on this subject which analysed data of 69 cases of suspected Black Cohosh induced liver disease, highlighted the poor quality of these cases, most of which were spontaneous reports as opposed to published case reports [22].

A meta-analysis of five clinical trials involving administration of an isopropranolic Black Cohosh extract in 1,117 women over a 3 or 6 month period for any effect on liver function, has recently been published[24]. Trials involving products extracted with solvents other than isopropanol were excluded by the authors, who were sponsored by the manufacturer of isopropanolic Black Cohosh extract. The authors found no evidence of adverse effects on liver function, as determined by measurement of liver enzyme levels at the start and end of Black Cohosh treatment at daily doses ranging from 40 to 128mg of the extract [24].

While rare cases of Black Cohosh induced idiosyncratic liver damage may occur, this latest study adds further weight to the growing body of evidence suggesting that the association of this herbal medicine with adverse effects on the liver is somewhat contentious.

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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 $\alpha\alpha$-amylase enzymes, key enzymes relevant to diabetes mellitus[9].

Possible applications of Ginger in diabetes have been further explored recently, 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 LD50 of both Ginger extracts used, were also determined.

Both extracts showed a very good safety profile, with calculated oral LD50'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

Ginger

diabetic rats[11]. A marked decrease in 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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Ginkgo Protects Against Gentamycin Induced Ototoxicity

Based upon favourable reports from open clinical trials in the 1980's[1,2], leaf extracts of *Ginkgo biloba* were once widely promoted as being useful for tinnitus and other hearing disorders. However the enthusiasm once seen for such use has fallen since results from a twelve week controlled trial involving 360 participants published in 2001 found no difference between Ginkgo and placebo treated groups[3].

It has however been suggested that the dosage used in this trial (120mg per day of extract equivalent to 6g of dry leaves and standardised to 28.8mg of Ginkgo flavonoid glycosides and 7.2mg of terpene lactones), was perhaps too low to achieve a significant outcome[4]. This premise is supported by results from a German trial involving 60 tinnitus inpatients initially given 10 days treatment with parenteral Ginkgo followed by outpatient oral treatment. This found improvements in both the tinnitus volume as well as secondary outcome measures such as decreased hearing loss and improved self-assessment of subjective impairment[5]. The type and duration of tinnitus could also influence the response to Ginkgo treatment with disorders of recent as opposed to long-term duration appearing to be more responsive[6-8].

Unfortunately further clinical trials to evaluate the possible influence of these factors during Ginkgo treatment for tinnitus have not yet taken place. The potential contribution of hypercholesterolaemia to development of inner ear disorders such as tinnitus led to a recent small clinical trial comparing 120mg Ginkgo extract daily to 40mg simvastatin treatment, over a 4 month period. In this trial no significant difference between groups, or between the pre- and post-treatment tinnitus scores in either group was found[9]. Despite

Ginkgo

Ginkgo

the negative findings from these trials using Ginkgo as a treatment for tinnitus, evidence of potential protective effects against ototoxicity induced by the aminoglycoside antibiotic gentamycin has recently been reported by Taiwanese researchers[10].

Gentamycin is a relatively cheap and widely used antibiotic, but long-term use can lead to nephrotoxicity and ototoxicity[11,12]. The latter manifests as hearing loss, tinnitus, vestibular damage and vertigo, all problems which involve overproduction of reactive oxygen species (ROS) and reactive nitrogen species such as nitric oxide (NO) in the early stages[12,13,14].

Based on its antioxidant properties and reputation for usefulness in tinnitus, the Taiwanese team set out to determine whether Ginkgo had any protective effect against gentamycin-induced ototoxicity, using both *in vitro* and *in vivo* methods on guinea pigs and rats.

The damage produced by gentamycin to *in vitro* cultures of rat cochlear hair cells was characterised and measured. These cellular changes were significantly reduced following pre-treatment with Ginkgo extract, some in a dose-dependent manner. Administration of Ginkgo also reduced ROS production and NO levels in the cochleae down to levels of non-gentamycin treated cochleae.

Another study was undertaken involving guinea pigs with gentamycin-induced hearing damage. Various parameters were measured in gentamycin treated and untreated ears, and oral administration of Ginkgo extract (100mg/kg/day) for 2 days prior to gentamycin injection prevented damage on several levels. These included reversal of the elevations in auditory brain stem response threshold, ratio of cochlear hair cell damage, and apoptosis as measured in the control group.

Finally, the effects of various Ginkgo constituents (kaempferol, quercetin, bilobalide, Ginkgolide A and Ginkgolide B) on gentamycin cochleotoxicity were compared with those of the Ginkgo leaf extract itself. Prevention against gentamycin-induced hair cell damage was exhibited by all compounds except kaempferol.

Despite being an animal study, this latest investigation into Ginkgo's possible actions as a preventative agent against a serious drug induced adverse effect is of great interest. Like other types of neurological damage, significant restoration of nerve and organ functionality following ototoxicity appears to be an unlikely treatment outcome and prognosis depends on the patient's age, underlying medical conditions if any, as well as degree of nerve damage. While Ginkgo treatment in such patients may not hold much promise, Ginkgo taken as a prophylactic by at risk individuals could potentially produce significant benefits.

Evidence is mounting that the traditional view of Ginkgo as a cognitive enhancing herb with anti-dementia properties is perhaps somewhat exaggerated, or at least grossly over-simplified. Much of the published research on this herb during the past few years relates to its effects as an adjunctive agent helping to protect against drug-related adverse effects[15]. These potential benefits include as an adjuvant treatment in schizophrenic patients taking the antipsychotic drug haloperidol[16], protection against male infertility during chemotherapy treatment[17,18], and protection against doxorubicin-induced heart damage[19].

Given the serious impact of hearing damage both to patients and health budgets, a clinical trial in humans to determine whether Ginkgo can help prevent gentamycin-induced ototoxicity would now seem warranted.

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Cardiovascular Benefits of Hawthorn

Hawthorn berries, leaves and flowers have been used as medicine for many centuries, with Culpeper's 16th century herbal recommending Hawthorn for kidney and bladder stones and dropsy. Other traditional uses were for fever, pleurisy, nervous tension, insomnia and depression, but for the past 100 years or so interest in Hawthorn has become increasingly focused on its effects on the cardiovascular system. Main indications claimed by herbal therapists include heart failure, angina pectoris, coronary artery disease, hypertension and cardiac arrhythmias[1].

In Europe and English speaking countries, two main species are used, *Crataegus monogyna* (Common Hawthorn) and *Crataegus laevigata* (also known as *Crataegus oxyacantha*).

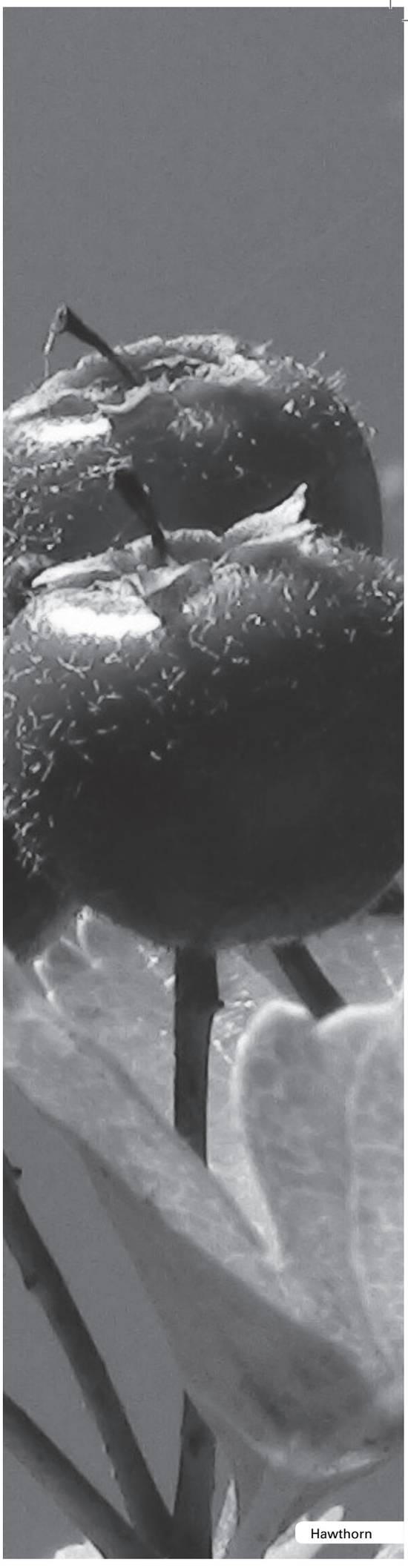
Most scientific studies to date have focused on Hawthorn's role as a possible treatment for chronic heart failure, with convincing evidence now existing for some benefit in mild forms of this disease[1]. Encouraged by these findings, its influence on other cardiovascular disease parameters has also begun to attract interest from researchers.

Coronary or ischaemic heart disease (CHD) is a condition characterised by lack of blood flow through the coronary arteries, usually as a result of atherosclerosis, which can lead to chest pain, angina, or a myocardial infarction. It is one of the most common causes of sudden death in adults, with risk factors including a hereditary predisposition, hypercholesterolaemia, obesity, hypertension and smoking. It's occurrence in patients with diabetes mellitus is also high.

A randomised double blind placebo controlled clinical trial was held recently in Spain to explore Hawthorn's effects in diabetic patients with CHD [2]. A total of 49 subjects aged between 45 and 75 years old with diabetes and chronic CHD were randomly assigned to receive either placebo or an extract made from the flowers and leaves of *Crataegus laevigata*, over a six month period. The Hawthorn preparation used was standardised to contain 5% procyanidins and 2% flavonoids, and taken at a dosage of 400mg three times daily.

Each subject had received a prior diagnosis of unstable angina or myocardial infarction, and had at least one significant coronary lesion, revascularised or not. All participants had been asymptomatic within the previous six months, and no changes had been made to their hypolipidaemic or hypotensive drug treatment for at least 3 months before the study commenced. All were taking aspirin, and most were on statin, ACE inhibitor and/or beta-blocker medications.

When bloods and biochemical parameters were analysed at the end of the 6 month treatment period no changes were seen in haemoglobin, erythrocytes, platelets or leukocytes including neutrophils, nor in plasma concentrations of urea, creatinine or electrolytes. No significant change was measured in levels of malondialdehyde (an expression of lipid peroxidation) or C-reactive protein between treated and placebo groups at the study's completion. In the Hawthorn treated group, however, statistically significant reductions


Hawthorn

in blood concentrations of total cholesterol and LDL-cholesterol from baseline levels were measured. While failing to reach statistical significance, a trend to lower total cholesterol was also identified in the Hawthorn versus placebo treated group.

This trend to reduce total cholesterol, LDL cholesterol and non-HDL cholesterol, is interesting given the relatively small number of participants in this study, as well as the fact that it was measured in patients on statin drugs with low baseline cholesterol levels. The possibility of a beneficial interaction with statins therefore cannot be ruled out.

Previous studies have also shown *in vitro* inhibition of neutrophil elastase by Hawthorn[3,4]. This enzyme is thought to have a role in the formation, progression and thrombotic complications of atherothrombosis[5]. Patients with angina pectoris with high leukocyte elastase levels have also been shown to be at increased risk of thrombotic cardiovascular events[6], and high plasma elastase has been reported in cardiomyopathy and following acute myocardial infarction[7,8]. Inhibition of neutrophil elastase has been shown to protect against myocardial dysfunction following ischaemia in studies on pigs[9].

In the Spanish study, three patients in the placebo group and two patients in the Hawthorn group presented with higher levels of plasma neutrophil elastase. At completion of the study these high levels had returned to normal in the Hawthorn group but not in the placebo group, a difference that was statistically significant. Figures decreased from 35.8 to 33.2ng/ml in the Hawthorn treatment group, but rose from 31 to 36.7ng/ml in the placebo group.

This study shows that Hawthorn appears to be safe and well tolerated when taken by diabetic patients with chronic CHD also taking conventional medication, and that beneficial effects on the blood lipid profile as well as possibly useful reductions in elevated plasma elastase levels may occur. Larger studies to further explore these benefits in chronic CHD patients therefore seem justified.

Leaves of the closely related Chinese Hawthorn *(Crataegus pinnatifida)* have also recently been shown to have favourable effects on lipid and glucose regulation in rats and mice[10], and to reduce balloon catheter-induced neointima formation in rat carotid arteries[11]. Additionally, in Turkey antithrombotic effects have been reported for an ethanolic extract of leaves of *Crataegus orientalis,* using a carrageenan-induced mice tail thrombosis model[12].

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