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## Black Cohosh reduces the risk of breast cancer?

**While protective effects of diets rich in phytoestrogens against the risk of breast and prostate cancer have been suggested by epidemiological studies[1,2], speculation as to the possible effects on breast cancer risk of phytoestrogens and other plant compounds used as natural alternatives to HRT, has mounted in recent years.**

The root of the north American herb black cohosh (*Cimicifuga racemosa*), has shown particular promise as a treatment for menopausal symptoms, although seems to act more of an oestrogen receptor modulator rather than possessing oestrogenic or anti-oestrogenic activities[3,4].

Concern about the safety of black cohosh supplements occurred following release of results of a study at Duquesne University in the U.S., which suggested black cohosh increased the risk of metastases to the lungs in mice bred to spontaneously develop mammary tumours[5]. The frequency of new breast cancer tumours, however, didn't increase in the black cohosh treated mice, and extrapolation of these results to the human situation is obviously limited. It is also notable that despite being reported to a meeting of the American

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PHYTOmed™ medicinal herbs ltd.
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P.O. Box 83068
Edmonton, Waitakere 0652
New Zealand
Tel (09) 828 0040
Fax (09) 828 0039
Freephone 0508 PHYTOMED (749 866)

# Black Cohosh reduces the risk of breast cancer?

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Association for Cancer Research in 2003 and receiving much publicity at the time, no publication of these findings in a peer-reviewed journal has occurred to date.

In contrast to the Duquesne study, many *in vitro* studies using human breast cancer cell lines have reported that black cohosh can inhibit breast cancer cell proliferation[6-11]. These effects have been observed on both oestrogen receptor-positive and oestrogen receptor-negative breast cancer cell lines through induction of apoptosis or cell death[7-12]. They also withstand simulated liver metabolism, suggesting that similar effects may occur following oral administration[7,8].

More recently, potentiation of the *in vitro* anticancer effects of tamoxifen[13] and the chemotherapy drug doxorubicin[14], has been reported for black cohosh extracts. The black cohosh triterpene glycoside actein, also enhances the cytotoxic effects of the chemotherapy drugs 5-fluorouracil, doxorubicin and paclitaxel on human breast cancer cells at relatively low concentrations[15]. Evidence of possible benefits in the prevention or treatment of prostate cancer, is also growing[16-21].

**Recent studies in humans**

Adding further to this debate, findings from two recent human studies undertaken by German and American researchers, are of great interest[22, 23]. These were both retrospective studies, and examined the risk of breast cancer or breast cancer recurrence in women who had taken black cohosh.

The first of these was a company-sponsored cohort study which examined data from 18,861 breast cancer patients treated at a variety of locations in Germany[22]. The main endpoint was disease-free survival in the period following a diagnosis of breast cancer, with the mean time from diagnosis until data analysis being 3.6 years.

Outcomes in the 1,102 patients who had received therapy with an isopropranolic extract of black cohosh, were compared to those in the control group who had not taken black cohosh. While it took 2 years following initial diagnosis for 14% of the control group to have developed a recurrence, it took 6.5 years for recurrence to develop in the same proportion of the black cohosh-treated group. When other possible confounding factors were taken into account, the risk of recurrence in women who had taken black cohosh was found to be 83% that of the nonusers.

The other study was a population-based case-control study conducted by a team of researchers based at the University of Pennsylvania School of Medicine in the U.S.[23]. This involved 949 breast cancer cases and 1,524 controls, selected randomly from three local counties. All were African American or European American women aged between 50 and 79 years old and had been diagnosed with breast cancer for the first time between 1999 and 2002.

This study obtained data concerning the use of at least 17 different "hormone-related" complementary medicines, including black cohosh, ginseng, red clover, dong quai, isoflavones, yam creams, and soy medications. These had been used at least three times a week for one month or more prior to the date of diagnosis for the cancer patients, or date of telephone interview, for the control subjects. Many possible confounding factors such as age, education, age of first live birth, menopause status and family history of breast cancer were taken into account in matching controls to cancer cases, although dietary and exercise factors were not fully considered.

A total of 16% of women in the study reported use of any hormone-related supplement. Of these, 76 women in the control group versus only 25 of those who had been diagnosed with breast cancer for the first time, had taken black cohosh.

The risk of breast cancer was significantly lower among women who reported using any of the hormone-related supplements when compared to those who had not. Of the various preparations used, however, black cohosh was the only one significantly associated with a decreased risk of breast cancer, with an overall reduction of risk of 61% being observed[23].

Further analysis was undertaken to determine whether these chemopreventative effects associated with black cohosh use were related to the hormone receptor characteristics of the breast cancer. This suggested that protective effects seemed to be greatest against oestrogen receptor-negative rather than oestrogen receptor-positive forms of tumour, although this finding failed to reach statistical significance. A lower incidence of progesterone receptor-positive tumours, however, was more significantly associated with black cohosh use than progesterone receptor-negative types, with a reduction in risk of 64% versus 38% respectively.

The authors call for further research before these suggested preventative effects of black cohosh can be positively confirmed. Nevertheless, these two studies provide probably the best evidence to date, that black cohosh may provide a substantial level of protection from breast cancer in older women.

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# Black cohosh more effective than fluoxetine for menopausal symptoms

**Usage of herbal medicines to relieve the symptoms of menopause has increased during recent years, particularly since the risks of adverse effects such as breast cancer and thrombosis from hormone replacement therapy (HRT), have become apparent[1,2]. Of the many natural products promoted for menopause, black cohosh (*Cimicifuga racemosa*) root has become one of the most widely used. Several reviews on clinical trials involving this herb, have also found it to show particular promise as an alternative to HRT[3-5].**

Despite or perhaps to some extent because of this, critics of the value of herbal management of menopause continue to abound. Clinical trials where black cohosh has not been found effective in relieving menopausal symptoms, have also taken place, however the methodological flaws of these including their use of doses much lower than those traditionally used by medical herbalists, should be acknowledged[6-8].

Since the demise in popularity of HRT, few alternative drug-based protocols for the treatment of menopausal symptoms have been developed. Conventional management has often tended to be limited to the use of antidepressant drugs, such as selective noradrenaline reuptake inhibitors or serotonin reuptake inhibitors such as fluoxetine or paroxetine[9-11]. The latter are used particularly to treat hot flushes in women with a history of breast cancer, in whom HRT is contraindicated.

This protocol seems to be gaining in popularity, despite one study finding that fluoxetine had little effect on hot flushes[12], and the absence of proof of efficacy for other SSRIs such as sertraline[13]. Use of SSRI's is also associated with a risk of adverse effects, such as sexual dysfunction and suicidal behaviour.

Results from a Turkish study which compared the efficacy of black cohosh with fluoxetine in the treatment of women with postmenopausal symptoms, are therefore of interest[14]. This involved 120 healthy women who were divided into two groups, one who took 40mg black cohosh extract and the other a daily dose of 20mg fluoxetine, over a six month period. Each woman was asked to complete a daily diary to record the number and severity of hot flushes and night sweats. Evaluations were also performed at the end of the first, second, third and sixth months of treatment, at which the women subjectively graded the severity of each complaint. A combined questionnaire was also prepared, which included the recognised evaluation methods of a modified Kupperman Index, Beck's Depression Scale, and the RAND-36 Quality-of-Life questionnaire. This was completed at the commencement of the study and again after three months of treatment.

At three months, both the Kupperman Index (a subjective measure of common menopausal symptoms) and Beck's Depression Scale results decreased significantly in both groups. The decrease in Kupperman score was, however, significantly greater in the black cohosh-treated group compared to the fluoxetine-treated group, while that in the Beck's Depression Scale was greater in the fluoxetine than the black cohosh-treated group. Hot flushes and night sweat scores were reduced significantly in both groups after six months of treatment, but this improvement was more marked in the herbal than in the drug-treated women (85% compared to a 62% reduction). No differences between the two groups in the RAND-36 questionnaire were observed.

These results show that the black cohosh treatment used in this trial, produced a greater overall alleviation in menopausal symptoms than the antidepressant drug fluoxetine. However, while some improvement in feelings of depression was seen following black cohosh treatment, these particular symptoms were more effectively treated by fluoxetine.

**Combination with St John's Wort**

Findings from two further clinical trials undertaken recently, support the use of St Johns wort in combination with black cohosh for menopausal symptoms[15,16].

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# Black cohosh more effective than fluoxetine for menopausal symptoms

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The first of these was a multicentre Korean study, involving combined black cohosh and St John's wort treatment in a group of 89 peri- or postmenopausal women experiencing climacteric symptoms. At four weeks following commencement of treatment, this combination was found to be significantly more effective than placebo in alleviating climacteric symptoms, as evaluated by the Kupperman Index and hot flushes scores[15]. An additional slight increase in HDL-cholesterol levels was also measured in the herbal treatment group after twelve weeks, suggesting additional possible beneficial effects on lipid metabolism.

The second was a large German observational study, involving 6141 women who were prescribed herbal treatments for menopause by gynaecologists at 1287 outpatient clinics[16]. Black cohosh alone was generally prescribed for typical menopausal-associated neurovegetative symptoms such as hot flushes, headaches and mild mood changes, while a fixed combination of black cohosh and St John's wort was chosen for patients with more pronounced mood complaints. Patients were monitored for six to twelve months, and changes in symptom scores from baseline values recorded, with the primary outcome measure being the Menopause Rating Scale (MRS) and subscore PSYCHE. Reductions from baseline values were observed with both treatment regimens for all variables, but the combination therapy was slightly superior in terms of improvements in the primary variable. Possible adverse effects were reported in 0.16% of patients, and these were all non-serious.

These recent trials add further to our knowledge about how optimally to use black cohosh, and to evidence of its effectiveness in the alleviation of menopausal symptoms.

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# Clinical trial on herbal practitioner treatment of menopausal symptoms

**While an increasing number of clinical trials have assessed individual herbal or other CAM interventions for various human health conditions during recent years, few have appraised the value of practitioner-directed treatments. These are invariably individualised and varied according to the particular patient, rather than involving a standard or uniform protocol.**

This attribute of CAM practitioner treatments, makes them considerably more difficult to evaluate than conventional treatments involving single drug agents or other standardised approaches. With numerous possible confounding factors known to have potential relevance to the outcomes of clinical trials, a detailed appraisal of these and implementation of appropriate controls, is required in order to obtain meaningful results.

A clinical trial which investigated the effects of treatment of menopausal symptoms by qualified medical herbalists, whose findings were recently published in the journal *Family Practice*, is therefore of great interest[1]. This was a pilot prospective, randomised trial involving 45 women participants aged 46 to 59, who had experienced self-defined menopausal symptoms and no menstrual bleeding for the previous three months.

Patients were selected randomly from an urban UK GP practice database, with those who were taking hormone replacement therapy, the contraceptive pill, the anti-oestrogenic drug tamoxifen, complementary treatment for menopause, or psychiatric treatment, being excluded. Participants were randomised into fifteen women in the treatment group, and thirty women in the control group.

The treatment group received a care package from one of three qualified and experienced herbal practitioners over a five month period. These were all British-trained western medical herbalists who had previously determined that their treatment methods were very similar.

A full clinical history was taken at an initial one hour consultation. Depending on the presenting symptoms, constitution and other health problems, a care plan including diet and lifestyle advice was prepared for each patient. An individualised herbal treatment was also selected and dispensed at the end of this consultation. As is usual amongst western medical herbalists, the makeup of this was then adjusted as required during subsequent consultations, depending on patient progress and any reported changes. Patient compliance and reported adverse effects, were recorded at each consultation. Each patient received a total of six consultations from the same practitioner over a period of 18 weeks, and took the herbal medicines prescribed during these visits, for a 24 week period.

Outcome measures were based upon two patient self-assessment questionnaires, the primary one being the Greene Climacteric Scale, a validated measure of menopausal symptom severity consisting of 21 questions with responses scored both totally and as four separate subscales. These include vasomotor (hot flushes and night sweats), psychological and somatic symptoms, and loss of libido. A further patient assessment system (MYMOP2) developed for use in complementary medicine which allows patients to identify their two most troublesome symptoms, and includes a well-being score, was used as a secondary outcome measure.

**Favourable results**

By eight weeks following commencement of treatment, a noticeable reduction in Greene scores for the treatment group was recorded. After 24 weeks, falls were seen in both the total Greene score and in all subscales, with particular improvement observed in vasomotor symptoms and libido scores. While reductions in scores were reported in both the control as well as the treated group, effects were significantly more marked in the treatment group, the total Greene score reducing from a baseline mean of 20.57 to 9.29 at 24 weeks, compared to a lesser drop

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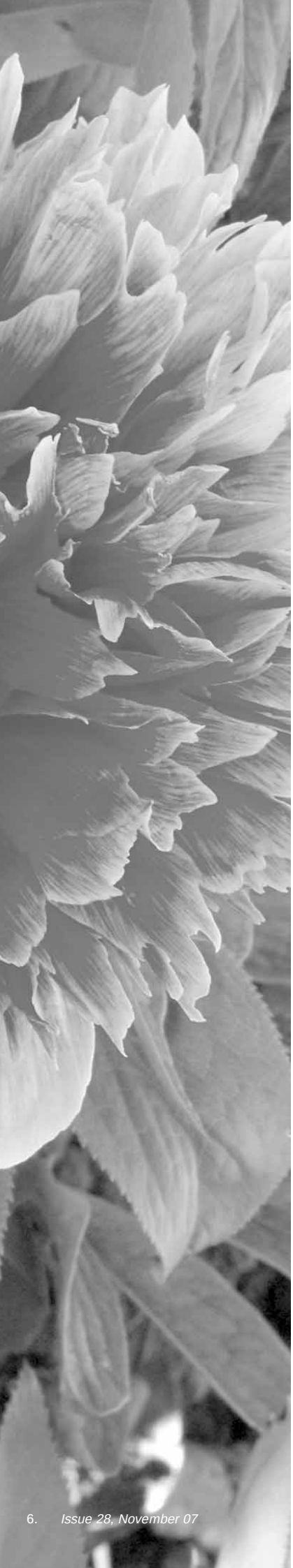

# Clinical trial on herbal practitioner treatment of menopausal symptoms

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from 22.34 to 19.62 in the control group. This 9.05 points greater drop measured in the treatment group was statistically significant ($P < 0.001$).

Reduced MYMOP2 scores were also obtained in the treatment group, who identified vasomotor symptoms as the most troublesome menopausal symptom.

A total of 58 herbs were used by the three practitioners when treating women in the treatment group, with an average of six different herbal extracts being used per prescription. Lifestyle and dietary advice was also provided at 61 of the 84 consultations.

This study has obvious limitations in its small size, and the fact that the waiting list methodology used for the control arm did not involve a placebo or address the possible bias associated with practitioner contact alone. Evidence exists in fact, that any therapeutic attention may cause some reduction in the incidence or perceived severity of menopausal symptoms, due to the psychological contribution to these[2].

The possibility that raised participant expectations could have had some influence, is suggested also by the fact that 36% of the treatment group and 30% of the control group had consulted a herbalist in the past. These levels are considerably higher than the likely consultation rate among the population as a whole[3].

However, with the primary aim of the study being to evaluate the treatment effect of herbal practice as a whole rather than separating out its individual components, as well as the fact that other recently published clinical trials have used a waiting list control group[4], this methodology does seem to have value.

This appears to be the first trial involving overall treatment by qualified western herbal practitioners, published in a peer reviewed journal. While small and not without methodological limitations, the dramatic improvement seen in these women, suggests that herbal practitioner-directed treatment of menopausal symptoms, has much to offer.

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# Favourable meta-analysis for Echinacea

**Echinacea was traditionally used by north American Indians for a wide range of ailments such as cold, influenza, insect and snake bites and cancer, and has become one of the most popular herbal medicines in developed countries in recent years[1-4]. In the US alone, more than 500 different products are available[5].**

Despite the widespread use of Echinacea as an immune stimulant, clinical trials to assess its efficacy in the prevention or treatment of colds or influenza, have produced mixed results. Thus while some studies into the effects of Echinacea products on the common cold or upper respiratory tract infections have produced favourable findings, others have failed to do so[6-9].

As often occurs when trials involving herbal products fail to find efficacy, the popular media tends to have a field day, and sweeping statements such as 'scientists have found no benefit from….', are invariably circulated rapidly and widely through global press agencies following publication of the results. Echinacea has been particularly savaged by such adverse press during the past few years, with negative findings from two poorly designed clinical trials in particular, achieving widespread publicity[10,11].

It was therefore a refreshing change to have had the positive conclusions of a meta-analysis of Echinacea trials, disseminated in a similarly widespread manner, in late June[12].

The meta-analysis, by researchers at the School of Pharmacy at the University of Connecticut, involved the pooling of results from 14 different clinical trials which evaluated Echinacea-containing products in the prevention and/or treatment of the common cold.

Duration of illness was treated as a continuous variable and the weighted mean difference was calculated as the difference between the mean days of the common cold in the Echinacea versus control groups. Numerous subgroup analyses were done to assess sources of clinical heterogeneity, and Echinacea's efficacy was assessed both in the presence and absence of other nutraceuticals, to allow for possible interactions. Separate analyses were done to evaluate studies which examined patients who were exposed to or contracted a cold either naturally, or through intentional inoculation.

While 738 citations for Echinacea were identified in the literature, only 73 were human clinical trials, but 59 of these were excluded due to there being no usable endpoint reported or not being placebo-controlled. Of the remaining 14 studies, 7 reported cold incidence, 5 cold duration, and 2 both cold incidence and duration. A total of 1356 study participants for cold incidence, and 1630 participants for cold duration, were included.

Seven of the trials involved monotherapy with *Echinacea purpurea*, one *Echinacea angustifolia*, one *Echinacea pallida*, one with an unspecified species of Echinacea, and four a combination of different Echinacea species.

The meta-analysis of these 14 trials, showed that Echinacea decreased the odds of a patient contracting a cold by 58% (OR 0.42, 95% confidence interval 0.25-0.71; Q statistic $p<0.001$). The duration of a cold was also found to be reduced by 1.4 days due to Echinacea use ($p=0.01$). Comparison of the results on duration of cold in the overall analysis to the subgroup analyses of Echinacea combined with other supplements, suggested that the benefits were caused by Echinacea rather than the other supplements.

Prophylactic use of Echinacea resulted in a 65% drop in incidence of natural colds compared to placebo, whereas when it was given as prophylaxis against cold induction caused by direct rhinovirus inoculation, the incidence was only reduced by 35%.

This meta-analysis differed somewhat from a previous one by Melchart and colleagues published in 2000[13] and updated in 2005[14], which showed a benefit of Echinacea for the treatment but not prevention of a common cold. Thus additional benefits were suggested for Echinacea in both the prevention and

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# Favourable meta-analysis for Echinacea

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treatment of a cold. Unlike the Melchart review, unpublished evaluations were excluded, but studies using experimental rhinovirus inoculation or Echinacea combined with other nutraceutical ingredients, were included. Cold severity was also excluded as an outcome measure, because of concerns about the potential heterogeneity of the methods used for cold severity assessment.

The authors conclude that the evidence suggests that Echinacea has a benefit in decreasing the incidence and duration of the common cold, but call for large-scale randomised prospective studies controlling for variables such as species, quality of preparation and dose of Echinacea, method of cold induction, and objectivity of study endpoints.

Perhaps more than most herbal medicines, clinical trials involving Echinacea have unfortunately involved an extremely wide range of products, including those made from individual or combined species, fresh or dried plant, and aerial parts and/or root.

Reference to the most authoratitive texts concerning the traditional use of Echinacea by north American Indians, shows that they had a strong preference for using the root[15-17]. These also tend to contain higher levels of immunostimulant phytochemicals known as alkylamides (alkamides), which recent research shows have good bioavailability following oral administration of Echinacea preparations[18-21].

While this meta-analysis is a welcome boost for the validation of Echinacea's effectiveness in both the prevention and treatment of colds, it contains little discussion or subanalyses into the possible influences of the type of Echinacea preparation used in the trials appraised, or the dosage used. Such investigations should add significantly to our knowledge about how to optimally use these valuable plants as medicines.

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# Bronchodilatory and other respiratory tract effects of Thyme

**Extracts of Thyme (*Thymus vulgaris*) are widely used by herbal practitioners for the treatment of conditions such as bronchitis, upper respiratory tract infections, laryngitis, tonsillitis, asthma and chronic obstructive pulmonary disease, now known as recurrent airway obstruction (RAO). A number of recently published papers, have added to evidence for the potentially beneficial effects of this common herb for these respiratory tract conditions[1,2,3].**

Smooth muscle relaxant effects for thyme were first reported by Scandinavian researchers in 1962[4], with subsequent investigations showing that both volatile oil and flavonoid components have spasmolytic effects on tracheal muscle[5,6,7,8]. These implied the possibility of a bronchodilatory effect by thyme, supporting its usefulness in asthma or RAO.

Several possible mechanisms exist for bronchial smooth muscle relaxant effects of thyme. Bronchodilatory drugs used for (asthma or RAO) generally act as agonists of $\beta_2$-adrenergic receptors (eg salbutamol), or inhibitors of acetylcholine receptors (eg ipratropium bromide). Comparable effects to those produced by the anti-asthma and β-adrenergic stimulatory drug theophylline on guinea-pig tracheal muscle, were reported by Iranian researchers last year[9]. Probable mechanisms suggested by these effects, using an aqueous thyme extract, were β-adrenergic stimulatory or anti-histaminic activities.

These effects were recently explored further, by a team of German researchers from the Institute of Medicinal Chemistry in Munster[2]. Using purified rat lung and uterine membranes in receptor binding and contraction experiments, they evaluated the effects of a patented extract of thyme, manufactured using glycerol, ethanol and water. Measurements of mucociliary clearance were also undertaken using an in vivo microdialysis method in mice[10].

Following pre-treatment with thyme, an increase in mucociliary clearance in mouse trachea was measured. In the receptor binding studies, a significant but relatively weak affinity of thyme was shown for $\beta_2$-adrenoreceptors contained within rat lung membranes. Tracheal contraction was also reduced directly by thyme, and its presence reduced the amount of the $\beta_2$-adrenoceptor agonist drug isoprenaline required to induce tracheal relaxation. A partial reversal of the antagonistic effect of the $\beta_2$-adrenoceptor receptor blocker drug propranolol on the relaxant effect of isoprenaline, was also seen.

The data from this German study thus show that the known spasmolytic effect of thyme on bronchial smooth muscle is probably mediated through both a direct relaxing effect as well as a modulatory effect on $\beta_2$-adrenoceptors, the net result being improved airways clearance. Increased ciliary activity and mucus transport also shows an additional expectorant action, potentially very useful in chronic bronchial conditions in which damage to the mucociliary transport system is prominent, and also shown to be at least partially due to its interaction with these receptors.

Anti-inflammatory and antioxidant effects of thyme extracts, are probably also useful in the treatment of various bronchial conditions (such as asthma and RAO)[11,12].

**Antibacterial effects and clinical trials**

Thyme essential oil also exhibits a broad spectrum antibacterial activity against respiratory tract pathogens, including antibiotic resistant species of *Bacillus cereus*, *Escherichia coli* and *Staphylococcus aureus*[13,14]. In a recent study in which 13 different essential oils were tested for their inhibitory effects against major respiratory tract pathogens, thyme and cinnamon oils showed the strongest inhibitory effects[3]. Antibacterial effects were measured against *Streptococcus pyogenes*, *agalactiae, pneumoniae* and *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Stenotrophomonas maltophilia*, all isolated from clinical specimens. The authors concluded that thyme seems the most promising oil of those tested, showing a marked antibacterial effect, despite a low cytotoxicity.

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# Bronchodilatory and other respiratory tract effects of Thyme

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These beneficial effects of thyme are further supported by various clinical studies involving administration of oral preparations containing thyme for the treatment of lung conditions. Reduced symptoms were measured in a group of 150 outpatients suffering from acute bronchitis, following treatment with a mixture of thyme and primrose root, over a 7-9 day period[15]. A double blind placebo-controlled trial involving 361 outpatients with acute bronchitis reported a significant reduction in coughing fits and other symptoms after 7 to 9 days treatment with an ivy and thyme syrup[16]. Another open trial involving a cough syrup containing ivy leaf extract, marshmallow root, aniseed and thyme, reduced symptom scores in a group of 62 patients with cough as a result of the common cold, bronchitis, or respiratory tract conditions associated with the formation of viscous mucus, when taken for an average 12 day period[17].

Two pilot studies have also taken place in horses, one involving an extract of thyme and primrose[18], and one a composite of garlic, white horehound, boneset, aniseed, fennel, liquorice, hyssop and thyme[19]. In the first of these a significant improvement in pulmonary pressure and airway resistance was observed in horses suffering from heaves[18]. While in the second study the trend to a reduced respiratory rate and increase in proportion of macrophages in horses with RAO failed to reach statistical significance, the multiple herbal nature of this product, and small number of horses used, were possible limitations in its design[19].

The collective evidence of these recent studies, gives strong support to the traditional use of thyme for a range of bronchial conditions associated with bacterial infection or recurrent airways obstruction.

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# Anticancer effects of Andrographis paniculata

**The shrub Andrographis (*Andrographis paniculata*) is highly regarded as a medicinal herb in India where it is known as kalmegh ('king of bitters'), and is also popular in China and other Asian countries. Principal traditional uses include for digestive conditions such as poor appetite, flatulence, dysentery and gastroenteritis, as well as hepatitis, diabetes, skin infections and fevers. Research over the past few years has also reinforced its traditional use for the treatment or prevention of a variety of infections and infestations, including those affecting the bowel, urinary tract and lungs, as well as the common cold[1,2]. Apart from its pronounced hepatoprotective properties[3], anti-inflammatory[4] and antidiabetic[5] activities have also been reported.**

With immunosuppression and the consequent impairment of the antitumour function of the immune system being increasingly linked with the onset of cancer, plant medicines that enhance or modulate natural immunity are now regarded as being potentially valuable in the chemoprevention of cancer, or as adjunctive treatments to conventional therapies[6]. Several scientific studies whose results have been published during recent months, support a potential role for Andrographis in this regard.

Evidence of potential protective effects against cancer for Andrographis was first reported in 2001. Investigators reported enhancement of antioxidant enzymes, plus numerous favourable modulatory effects on hepatic and extrahepatic carcinogen metabolising enzymes, in studies on mice[7].

Enhanced tumour necrosis factor alpha (TNF-$\alpha$) production, and thus cytotoxic activity of lymphocytes, was reported for andrographolide, a key bitter diterpenoid lactone constituent, in 2003[8]. While increased cytotoxic activity of natural killer (NK) cells, and TNF-$\alpha$ was reported in an uncontrolled study in humans in 2002[9], this involved concurrent administration of seven different natural products, and a contribution of Andrographis was therefore undetermined.

Recent studies in mice however, have confirmed both enhancement of NK cell activity, as well as antibody-dependent cellular cytotoxicity in both normal and tumour-bearing mice, for both Andrographis and andrographolide[10].

This same group of Indian researchers have published prolifically on this subject recently[10,11,12], including another paper reporting the effects of Andrographis extract and andrographolide on the production of cytotoxic T lymphocytes in mice[11].

Cytotoxic T lymphocytes are a subset of T cells that play a pivotal role in protection from tumours, causing both tumour lysis directly as well as producing interferon-$\gamma$, a cytokine with several direct and indirect antitumour properties.

Lymphomatous cancer cells (EL4) were incubated with alloimmunised spleen cells (effector cells) and administered to mice, resulting in an average survival of 35.8 days. Mice with this type of lymphoma showed decreased immune responses, especially of the cell-mediated type, and this was associated with impaired generation of cytotoxic T lymphocytes.

Following treatment with ten doses of 10mg Andrographis extract or 500$\mu$g andrographolide, survival rates increased to 52.1 and 48.1 days, with continued treatment for a further ten days increasing life spans to 62 and 53.8 days respectively. Levels of the cytokines interleukin-2 and interferon-$\gamma$ were also enhanced during treatment with both extract and andrographolide. The authors correlated this with increased activity of cytotoxic T lymphocytes, these being generated by the above two cytokines *in vivo*, and associated *in vitro* experiments showing that Andrographis and andrographolide enhanced their production[11].

Collectively, these results implicate a large contribution of andrographolide to the immunomodulatory effects of Andrographis, for which inhibitory effects

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# Anticancer effects of Andrographis paniculata

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on proliferation of a number of cancer cell types have been shown *in vitro*[8]. These effects seem to be mediated by both direct anticancer effects through cell-cycle arrest, as well as increased proliferation of cytotoxic lymphocytes through production of interleukin-2[8] and interferon-γ. Enhancement of TNF-α production resulting in increased cytotoxic activity of lymphocytes against cancer cells may also be contributory.

Andrographolide has also been observed by a group of Malaysian researchers to exhibit selective cytotoxicity to prostate cancer cells and induce apoptosis (cell death) through activation of caspase-3 and caspase-8 enzymes[13].

Results of work by Chinese researchers recently published in the journal *Anticancer Research*, found andrographolide decreased the ability of gastric cancer cells to adhere to human vascular endothelial cells. These effects were mediated by blocking expression of E-selectin by cancer cells and thus inhibiting tumour cell adherence, implicating a further possible mechanism for its anticancer activity[14].

Inhibition of angiogenesis (tumour microvascular growth) is another promising pathway to inhibit cancer cell growth. Another recent study in which treatment with Andrographis as well as andrographolide lead to a marked reduction in elevated levels of the angiogenic factor VEGF and increased the production of antiangiogenic factors in mice, is therefore of interest[12].

Clearly the diverse and positive findings on the anticancer properties of Andrographis and andrographolide are very encouraging. It seems possible that this plant could well be heading down the pathway of joining the several others from which cytotoxic drugs have been developed during recent decades. Several andrographolide derivatives with pronounced anticancer activities against a range of cancer cell types, have in fact been synthesised by Malaysian researchers recently[15].

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Written by Phil Rasmussen.


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