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Growing Problems with Microbial Resistance

Bacterial resistance to antibiotics has been a problem since soon after they were first introduced in the early 1940's, and despite much effort to manage this issue and develop new antibiotics, resistance continues to increase. The overuse of antibiotics has lead to rising rates of resistance among common pathogens such as *Streptococcus pneumoniae* and *Streptococcus pyogenes*, clinicians are finding it increasingly difficult to treat infections that were once easily overcome by a short course of any one of a number of antibiotics. Public health officials and hospital authorities also continue to engage in ongoing battles with outbreaks of the infamous methicillin-resistant *Staphylococcus aureus* (MRSA) strain of bacteria in hospital wards around the world. Recent figures from England and Wales show that around 800 deaths a year are linked to MRSA in these two countries alone, a 15 fold increase on a decade ago[1]. With the first cases of resistance to vancomycin, the antibiotic reserved primarily for MRSA, and the spread of MRSA to community settings, health authorities around the world are taking this problem increasingly seriously.

Continued page 2.

IN THIS ISSUE

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Growing Problems with Microbial Resistance

Continued from the front page.

While efforts to contain resistance through control of environmental risk factors, and less and selective use of antibiotics have been made in recent years, clearly much more needs to be done. The Center for Disease Control and Prevention (CDC) in the U.S. reported the consumption of 235 million doses of antibiotics in 2001, and estimated that 20-50 percent of these were unnecessarily prescribed for viral infections[2]. American infectious disease experts recently issued a press release stating "there simply aren't enough new drugs in the pharmaceutical pipeline to keep pace with the evolution of drug-resistant bacteria, the so-called superbugs"[3].

It is now acknowledged by many leading microbiologists that new approaches to the treatment and prevention of infectious diseases are required[4,5]. In retrospect, the development of resistance has been an inevitable consequence of antibiotic use through exerting a selective pressure among bacteria, encouraging the emergence of antibiotic-resistant strains by eliminating antibiotic-sensitive strains, and permitting the spread of resistant strains from infected individuals. Their introduction has in fact been a tremendous stimulation to the evolution of bacteria and appearance of new pathogenic strains[4,5,6,7].

INTER-SPECIES INFECTIONS

Emergence of other new highly dangerous genotypes of viruses such as the Hong Kong avian influenza outbreak of 1997, or SARS (Sudden Acute Respiratory Syndrome) in 2003, is another trend which has occurred in parallel with the emergence of antibiotic-resistant bacteria. While the exact vector of transmission remains unknown, interspecies transmission of bacteria or viruses appears to be increasing in frequency. The recent reemergence of 'avian bird flu' in Thailand, China, Vietnam and Indonesia highlights the ability of avian influenza strains circulating in wild birds to move into closely related domestic species, and subsequently become potentially dangerous to humans[8]. If such viruses were to mutate in humans also infected with a common flu virus, new highly virulent strains that could pass from human to human, could potentially be created[9].

Against this background, practices such as routine treatment of chickens with prophylactic growth-promoting antibiotics have met with growing criticism in recent years. In New Zealand, antibiotic use on animals remains at a very high level, despite research finding the presence of high rates of vancomycin-resistant bacteria in half the country's chickens[10]. The huge growth in use of antibacterial household products over the past decade, despite the absence of any evidence of improved health as a result, is an additional dangerous trend with the potential to catalyse development of resistant bacteria[4].

THE ROLE OF PHYTOMEDICINES

Prior to the introduction of chemical antimicrobial agents and antibiotics, phytomedicinal preparations were the principle methods used to help prevent and treat infectious diseases in humans. It is the author's opinion that phytotherapy could make a valuable contribution to a different approach to managing such diseases, in order to help minimise the development of microbial resistance.

This concept is supported by a large volume of published research which has both validated traditional antimicrobial applications for numerous plants in animals and humans, and found evidence of new potential indications for them.

Antibacterial activity particularly against gram-positive types of bacteria, has been shown in vitro for a large number of different phytomedicines and their preparations[11,12,13,14]. Antifungal[15,16,17,18] and antiviral[19,20,21,22,23] activities, as well as antiparasitical effects[24,13] are well documented for others, including against resistant microbes.

Immunostimulant activity mediated through a non-specific enhancement of the phagocytic abilities of macrophages, is mediated by plants such as Echinacea, Astragalus and Ginseng[25,26,27]. Efficacy for the treatment of common conditions such as colds and influenza, has been reported for several of these agents in clinical trials[19,25,26,27,28,29,30,31]. In all cases, the presence of phytochemicals with direct antimicrobial activities and/or immunostimulant properties, underlies these actions.

PHYTOMEDICINES AS ADJUNCTIVE AGENTS

Another area which also offers enormous potential is in the application of phytomedicines and plant-derived compounds as adjunctive therapy to be used in combination with antimicrobial drugs. The now well-known synergistic effects and improved clinical response often obtained through use of more than one antimicrobial agent concurrently to treat serious infections, strongly implicates similar benefits from such use of phytomedicines.

This concept is supported by findings of phytomedicine-induced potentiation of the antimicrobial activity of several antiviral[32,33,34,35,36], antibacterial[37,38,39], and antifungal[40,41] drugs.

Multidrug resistance, is a property conferred on microbial cells probably by a pump which extrudes toxins across their outer membrane, thus preventing entry through their outer membrane by antimicrobial agents. The ability of several plant extracts and phytochemicals to inhibit development of multidrug resistance, is an area which warrants more research. Promising results have already been reported where certain plant compounds such as 5'-methoxyhydnocarpin (from *Berberis spp*)[42], flavones from *Artemisia annua*[43] and *Lupinus argenteus*[44], and polyacylated neohesperidosides from *Geranium caespitosum*[45], have shown the ability to disable the multidrug resistance pumps of gram-negative bacteria, thus enhancing the penetration of antimicrobial agents into bacterial cells[42,43,45].

Recent studies where antimicrobial plant extracts were combined with such inhibitors of multidrug resistance, have also produced promising results[42].

In a modern clinical context, there is a growing evidence base of data that appropriate phytotherapy could be usefully applied both as a preventive or first line treatment for many common infections. It is clear that use of proven antimicrobial or immunostimulant phytomedicines, has enormous potential to reduce or avoid the need for antibiotic and other antimicrobial drug medication in many cases.

With the growing urgency to adopt fundamentally new approaches to infectious disease management in order to counter microbial resistance and prolong the shelf lives of life-saving and expensive antimicrobial drugs, the time for more work in this area, including clinical trials in humans, has now arrived.

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Eleutherococcus clinical trial for chronic fatigue

***Eleutherococcus senticosus* (Siberian ginseng) has been enormously popular in recent years for the treatment of chronic fatigue, and a large number of preparations, either prescribed by practitioners or available over the counter, contain this phytomedicine as a major ingredient. Evidence of adaptogenic properties (protection against biological and physical stressors) for Eleutherococcus has been documented from various *in vitro* and animal studies[1,2]. Relatively few clinical trials have however been conducted on humans to date, and those that have occurred have mainly been published in Russian journals and are not generally available in English-speaking countries. These have reported benefits in improving the ability to perform physical labour, the quality of proofreading, the speed and quality of work by telegraphers, the number of days lost to sickness among factory workers[2], and short-term memory in healthy humans[3].**

In more recent years, trials involving the influence of Eleutherococcus on various physiological parameters during exercise have produced somewhat mixed results[4,5,6,7]. No well-designed clinical trials to evaluate its efficacy as a treatment for fatigue had occurred until recently.

DOUBLE-BLIND TRIAL

Earlier this year, researchers from the University of Iowa published results of a double blind randomised controlled clinical trial to evaluate the effectiveness of Eleutherococcus in subjects suffering from chronic fatigue[8]. A total of 96 subjects were recruited from advertisements as well as chronic fatigue syndrome support groups, and were required to have substantial fatigue of at least six months duration with no identifiable cause.

Subjects took four 500mg capsules of placebo or an extract of Eleutherococcus standardised to provide an intake of 2.24mg per day of eleutherosides B and E, equivalent to a dried root dosage of 2 to 4g per day. Assessments for changes in fatigue measurements in the 76 patients who completed the trial, were made by questionnaire at one and two months.

Following the two months treatment, both the placebo and Eleutherococcus treated groups showed significant improvement, but no significant overall difference was measured between the two groups. However when patient characteristics used to subclassify fatigue were more closely evaluated, possible benefits in those patients with less severe fatigue of shorter duration, were demonstrated.

The authors of this study acknowledge its several limitations, such as the imprecise nature of 'fatigue' as an outcome measure and the diverse nature of the patients recruited, as well as the failure to examine the effects of different doses. Nevertheless the dose used in this trial was similar to that recommended by most phytotherapists (1-4g/day), although somewhat below the 6 to 12g a day recommended by some sources[9,10]. Most evidence of adaptogenic or stress-ameliorating effects for Eleutherococcus derives from animal studies or limited human studies conducted by Russian scientists in the latter half of the 20th century. It is significant that the dosages used in these studies were at least an order of magnitude higher than the upper limits of the recommended normal human dose[2,4,5,6,7].

BIPHASIC EFFECT IN STRESS

Another anomaly associated with this herb is a possible biphasic effect in terms of the stress response. Australian researchers demonstrated an Eleutherococcus-mediated inhibition of specific enzymes which limit the occupancy of both positive and negative feedback stress hormone receptors[11]. In a clinical trial on endurance athletes, the same researchers evaluated the effects of a six week course of Eleutherococcus (4g per day of a hydroethanolic extract) on steroidal hormone indices of stress (testosterone, cortisol and testosterone to cortisol ratio), and surprisingly found an increased rather than decreased stress response[12].

The authors of this study postulate that this may be consistent with animal research suggesting a threshold of stress below which Eleutherococcus increases the stress response, and above which Eleutherococcus decreases the stress response. This concept would however appear to conflict somewhat with that implicated by the Iowa clinical trial, whereby benefits were reported only in the subgroup of patients whose fatigue was either less severe or of more recent onset. It should of course be realised however, that chronic fatigue as a human complaint, is quite different as an outcome measure from exercise induced stress response in performance athletes.

While the Iowa researchers state that while their study does not demonstrate overall efficacy, it suggests that 'further evaluation of Siberian ginseng may be warranted for persons with moderate fatigue.

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Ginkgo - beneficial effects in liver disease?

***Ginkgo biloba* is well known for its beneficial effects on memory and cognitive brain function, and a large body of data from clinical trials now exists supporting the clinical usage of this phytomedicine as a preventative or treatment agent in a wide range of neurological and circulatory disorders. A beneficial effect on the circulation, as well as significant antioxidant properties, are thought to be largely responsible for these effects.**

Two studies whose findings have been published recently, reveal potential uses also for ginkgo as a preventative or treatment agent in serious liver diseases, including cirrhosis, fibrosis and hepatocellular carcinoma[1,2].

IN VITRO

The first study involved testing the effects of a standardised ginkgo extract on cell proliferation and cytotoxicity in human hepatocellular carcinoma cells *in vitro*[1]. Cell proliferation and cytotoxicity of the cancer cell lines (HepG2 and Hep3B) were determined after 24 hours incubation with various concentrations of the ginkgo solution, and expression of proliferating cell nuclear antigen and p53 protein were measured after 48 hours incubation. Ginkgo was shown to cause a 39 to 45% suppression of cell proliferation of both cell types compared to the control group, and to increase lactate dehydrogenase release from these cells. Reduced expression of proliferating cell nuclear antigen, and increased expression of p53 protein, was also produced by adding ginkgo to the HepG2 cell types.

While the ginkgo concentrations which produced these cytotoxic and proliferation-suppressing effects were relatively high (1000mg per litre), ginkgo flavones and terpenoids have relatively good oral bioavailability and travel straight to the liver following gastrointestinal absorption[3,4]. The results from this *in vitro* study therefore implicate the possibility that similar clinically significant benefits could well derive from the use of ginkgo in hepatocellular cancer patients, or in those with a high risk of developing this life-threatening condition.

IN VIVO

Further evidence of potential benefits for ginkgo in liver diseases was reported also by Chinese researchers recently. This second group of researchers found that administration of ginkgo to rats for four weeks was able to reduce the level of liver fibrosis[2]. These effects occurred in conjunction with reduced serum levels of bilirubin and aminotransferase, increased levels of serum albumin, and lower levels of liver collagen and reticulum. The authors speculate that this improvement in induced liver fibrosis could be attributed to ginkgo's effect as a tissue inhibitor of metalloproteinase (TIMP-1), and promoter of the apoptosis (cell death) of hepatic stellate cells.

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Black cohosh and endometrial cancer

Black cohosh has a long history of being used for menopausal complaints, and its popularity has increased as a result of recently published studies revealing serious adverse effects from long term use of synthetic hormone replacement therapy (HRT).

Various studies into the safety of black cohosh have been undertaken over the past few years. A recently published review on this subject concluded that specific black cohosh extracts are a safe alternative for women in whom oestrogen therapy is contraindicated, including in women with a history of breast cancer[1,2].

No evidence of oestrogenic activity for black cohosh has been documented, from both animal and in vitro cell culture studies conducted using mammary cells. No gene transcription or induction of cell proliferation was shown to be induced in these various studies. The evidence to date, indicates that in women with a history of breast cancer, black cohosh appears to be a safe alternative menopausal treatment to synthetic oestrogen containing HRT.

With the risk endometrial cancer also being significantly increased by unopposed oestrogen therapy in post-menopausal women[3], possible influences of black cohosh on risk factors for endometrial cancer also need considering.

RECENT TRIAL

German researchers have recently published results from a study into the effects of a standardized extract of black cohosh on an animal model of endometrial cancer[4]. Ectopic growth of the primary tumour as well as the incidence and localization of metastases were measured, following treatment with black cohosh alone or during combination treatment with the oestrogen antagonist drug tamoxifen.

Black cohosh was found to have no influence on the growth or metastasizing potential of the primary endometrial tumour in these studies. In contrast the drug tamoxifen, which acts as an oestrogen agonist on endometrial tissue, increased tumour growth and frequency of metastases. No evidence of any synergistic or antagonistic effects between combined black cohosh and tamoxifen treatment was seen, although this may have been influenced by the relatively high dose of tamoxifen used.

Despite the obvious methodological weaknesses in this study, it provides further support for the favourable safety profile of Black cohosh documented to date, and indicates that its use in patients with a risk of endometrial cancer, is likely to be safe.

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Anti-allergic activity for Black Cohosh?

Apart from its use in gynaecology, Black cohosh *(Cimicifuga racemosa)* was once widely used as a treatment for painful inflammatory joint conditions by North American Indians and early American physicians, and this use has since spread to other countries[1]. Anti-inflammatory activity has been reported for key constituents including ferulic acid and isoferulic acid, found also in the related *Cimicifuga heracleifolia* which is used as an inflammatory in Japanese traditional medicine[2,3]. Inhibition of macrophage inflammatory protein-2 (MIR-2) and/or interleukin-8 production, could account for these anti-inflammatory effects[3,4].

Korean researchers recently tested black cohosh for potential anti-allergic activity, using mast cell-dependent in vivo and in vitro models[1]. Oral administration of black cohosh extract was found to produce a significant inhibition of the anti-IgE-induced passive cutaneous anaphylaxis reaction, as well as histamine release from rat peritoneal mast cells. Inhibition of interleukin (IL-4 and IL-5) and tumour necrosis factor (TNF-alpha) mRNA induction in human leukaemia mast cells was also measured.

The results from this study reveal a possible anti-allergic potential for black cohosh, mediated through inhibition of histamine release and cytokine gene expression in mast cells.

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Artemisia annua – clinical trial for malaria

Aerial parts of the Chinese medicinal plant *Artemisia annua* L. (Annual or Sweet Wormwood; Qinghaosu) have long being used in China and nearby countries for the treatment of febrile illnesses and malaria. During the 1960's and 1970's scientists actively searched for new antimalarial compounds from Chinese traditional herbs, leading to identification of the sesquiterpenoid antimalarial compound artemisinin in *Artemisia annua* in 1971. Both artemisinin and several synthetic derivatives have subsequently been developed into a number of new efficacious antimalarial drugs during the past 20 years[1].

Despite such new drug development, malaria remains a major public health problem affecting hundreds of millions of people, particularly in tropical developing countries. The limited availability and affordability of pharmaceutical medicines in these countries, means that the majority of the world's population continues to depend on traditional forms of medical remedies to treat disease. Such traditional herbal preparations therefore appear to offer the best chance of managing this parasitical disease in poorer populations.

CLINICAL TRIAL

Results from a pilot clinical trial using a traditional tea preparation of Artemisia annua in the treatment of malaria, were published in the May issue of *Transactions of the Royal Society of Tropical Medicine and Hygiene*[2]. This involved 132 patients with uncomplicated malaria in a rural setting in the Democratic Republic of the Congo. Patients were given traditional tea preparations of *Artemisia annua* at doses of either 5 or 9 grams daily for a seven day period, and the established antimalarial drug quinine was used as a control.

Artemisia treatment was well tolerated, with less frequent adverse events reported than in the quinine group. Treatment resulted in a quick resolution of parasitaemia and of clinical symptoms. After seven days of medication, cure rates were on average 74% for the Artemisia preparations compared with 91% for quinine. However, recurrence rates and the return of symptoms following discontinuation of treatment were high in the Artemisia treated group. The authors concluded that while monotherapy with *Artemisia annua* cannot be recommended as an alternative to modern antimalarials, it deserves further investigation.

Associated pharmacokinetic studies undertaken by the same team, found that the traditional tea preparations of *Artemisia annua* contained only 19% of the usual clinical dose of pure artemisinin (500mg/day)[3]. This suggests that the usage of higher doses than used in this pilot study, or the development of higher artemisinin-containing plant varieties, as well as longer treatment periods, could enable higher cure rates to be obtained from such a traditional tea preparation. Other options well worth further investigation would include the usage of dosage forms prepared using ethanol as a solvent as in modern phytotherapy, and/or combination of such traditional herbal preparations with antimalarial drugs, to hopefully enable a synergistic antimalarial response to be achieved.

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Possible interaction between Baical Skullcap and cyclosporin

Baical Skullcap *(Scutellaria baicalensis)* root is widely used in Chinese herbal medicine, and has become popular with some western medical herbalists over the past decade or so. Interest in this phytomedicine has increased in recent years, catalysed by the large and growing amount of published research documenting hepatoprotective, anti-inflammatory, immunomodulatory, antioxidant and cancer-protective activities[1,2,3,4,5,6]. The flavone glycosides baicalin and baicalein are known to contribute to many of these impressive pharmacological activities, but several other types of phytochemicals, including a considerable amount of tannins, are also found in Baical skullcap.

Taiwanese researchers have recently evaluated the effects of Baical skullcap on the absorption and disposition of the immunosuppressant drug cyclosporin in rats[7]. Their results showed that co-administration of a decoction of this herb by oral administration produced a significant decrease in the bioavailability of cyclosporin when this was given orally, but not intravenously. Thus the Area Under the Curve (AUC) for cyclosporin plasma levels following oral administration of this drug was reduced by 55% following administration of a decoction of Baical skullcap at a dose of 1g/kg, and 82% when a higher dose of 2g/kg was given.

When baicalin and baicalein, the principle flavonoid constituents of Baical skullcap were given alone however, the AUC and thus bioavailability of oral cyclosporin was increased rather than decreased. No effect on the AUC for parenterally administered cyclosporin was measured.

These studies implicate a potential pharmacokinetic interaction between Baical skullcap and orally administered cyclosporin. This is likely to involve interference with the absorption of this drug from the gastrointestinal tract, by tannins or other non-flavonoid constituents of this phytomedicine.

The clinical significance of these findings are somewhat debatable, due to the very high doses of Baical skullcap used in this animal study. It nevertheless seems prudent to avoid giving this phytomedicine at the same time of day as oral cyclosporin, in order to avoid a potentially serious reduction in plasma levels and thus activity for this drug (commonly taken long term by patients following organ transplantation). It also seems likely that a similar Baical skullcap tannin-mediated impairment of the absorption of many other medications taken concurrently could occur. Therefore, until more is known, this precautionary advice should probably be given to patients taking any other prescribed medication in conjunction with this phytomedicine.

This study also suggests the need for pharmacokinetic studies in humans, in order to better determine the clinical significance of this potential interaction.

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Baical Skullcap synergistic antioxidant effects with grapeseed extract

Antioxidant effects are well known for grape seed extracts, and seem to be largely mediated through their content of proanthocyanidins. Use of extracts of Grape seed as a rich source of antioxidants for the prevention and treatment of a wide range of medical conditions, has become enormously popular in recent years.

The Chinese herb, *Scutellaria baicalensis* (Baical Skullcap), is a common ingredient of several prominent Traditional Chinese Medicine herbal formulations, and has exhibited activity in many interesting pharmacological studies and clinical trials. A growing body of data implicates possible chemoprevention against various cancers (see *Phytonews* 17[1]). Antioxidant effects have been shown in a number of different experimental test systems, including free radical scavenging properties, inhibitory effects on lipid peroxidation, and protection of neuronal cells exposed to oxidative stress[2,3,4,5,6,7,8].

Chinese researchers have recently found that a synergistic antioxidant response occurs through combining Baical skullcap with grape seed proanthocyanidins[9]. This finding was based upon tests using an in vitro model to produce reactive oxygen species, namely hydroxyl radicals and superoxide. This raises the possibility of a similar synergistic antioxidant effect being possible following their use as a combination for oral administration, thus enabling lower doses of each to be taken to produce similar effects, or a greater antioxidant response being achieved by the same dose of each substance.

Due to the potential for interactions between large doses of Baical skullcap and other drugs taken orally at the same time of day, which could reduce the gastrointestinal absorption of these (see previous article), it is probably advisable to take such a combination at a different time of day to other prescribed medication.

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Cinnamon for diabetes mellitus

Cinnamon bark has traditionally been used in the management of diabetes mellitus in its native Sri Lanka, yet until recently, no scientific evaluation of its reputed efficacy in this condition has taken place. Researchers based at an Agricultural University in Pakistan recently conducted a clinical trial involving its administration to people with type 2 (late onset) diabetes, in order to evaluate this alleged activity[1].

A total of 60 people with an average age of 52 years were given capsules containing 1, 3 or 6 grams dried cinnamon powder or placebo daily, and serum glucose and lipid levels were measured. After the 40-day treatment period, all three doses of cinnamon lead to a reduction in levels of mean fasting serum glucose (18-29%), triglyceride (23-30%), LDL cholesterol (7-27%), and total cholesterol (12-26%). No significant changes were seen in the placebo groups, or in levels of HDL cholesterol.

Other studies that have tested various plant extracts for possible insulin-like activities, found a high level of bioactivity for cinnamon[2,3,4]. Cinnamon extracts, as well as compounds derived from it, have shown the ability to enhance various *in vitro* effects of insulin[2,3,5,6]. These include activation of a form of insulin receptor and stimulation of insulin-dependant glucose reuptake[7], and reversal of insulin resistance[5,8].

Recent work aimed at characterising the insulin enhancing constituents from cinnamon identified water soluble oligomeric procyanidin complexes with antioxidant activity as having activity[9]. Insulin-like effects, including stimulation of glucose uptake and glycogen synthesis, have also been shown for a methylhydroxychalcone polymer (MHCP) found in cinnamon. A synergistic *in vitro* response was observed through dual treatment of adipocytes with this compound and insulin[6].

These studies show significant potential benefits of cinnamon in the control of glucose intolerance and diabetes mellitus, as well as associated hyperlipidaemia and cardiovascular disease. It seems likely also, based on this trial and the various *in vitro* studies to date, that cinnamon may also be a valuable tool for the treatment of insulin resistance in diabetic patients.

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Effects of Essiac and Flor-Essence on human cancer cells in vitro

Essiac tea and Flor-Essence are mixtures of various herbs (including burdock, slippery elm, sheep sorrel, and rhubarb), normally taken as an infusion, which are widely consumed by cancer patients around the world. They are taken either as part of a natural approach to the treatment of a wide range of malignancies, or in conjunction with conventional treatments such as radiotherapy and chemotherapy. The original recipe was first presented as an alternative treatment for cancer by Canadian nurse Rene Caisse in the early 20th Century, and it was said to have been passed on to her by an old Indian medicine man.

Despite their popularity, very little in the way of scientific evaluation of the potential anticancer or cytotoxic effects of either preparation has occurred to date, although experimental studies on the individual herbal components have shown evidence of biological activity, including antioxidant, antitumour, immunostimulant, antioestrogenic, and anticholeretic actions[1].

Researchers at the Center for Complementary Medicine Research in British Columbia, recently tested both teas for possible antiproliferative and differentiation inducing activities on various types of human tumour cells[2]. Various dilutions of each herbal tea were added to these cultivated cancer cell lines, and the concentration at which 50% inhibition of cell growth occurred (IC50) was measured. Cell lines tested included Jurkat leukaemia cells, MDA-MB-468 breast cancer cells, and promyelocytic leukaemia HL60 cells.

While both teas had an inhibitory effect on the growth of some cancer cell types at 1 in 10 dilution, at greater dilutions more representative of concentrations likely to be attained in a clinical (*in vivo*) situation (1 in 40 and 1 in 100), the cell cycle progression of all cell types was only slightly inhibited. The data obtained found that both teas demonstrated antiproliferative and differentiation inducing properties *in vitro* only at high concentrations.

This study thus did not find evidence of significant anticancer effects for Essiac and Flor-Essence® herbal teas *in vitro*, and indicates that further research is needed to elucidate their alleged activities in humans.

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Dandelion and cancer

Dandelion root is best known amongst Western phytotherapists for the treatment of a range of liver and gallbladder diseases, and as a bitter herb with beneficial effects on the liver. Traditional applications were widespread, with the name of the genus, *Taraxacum*, derived from the Greek *taraxos* (disorder), and *akos* (remedy), indicative of the widespread curative actions attributed to this plant. Dandelion has also been used in some countries as part of the treatment of breast and endometrial cancer[1].

Anti-tumour properties for dandelion were first reported in peer-reviewed literature by Japanese authors in 1981[2], although the first systematic investigations into its potential anti-carcinogenic activity were not published until 1999[3,4]. These studies found anti-tumour promoting activities and anti-tumour initiating activity for a dandelion root extract. Two triterpenoids (taraxasterol and taraxerol) were identified as having significant inhibitory effects on Epstein-Barr virus early antigen induction (known to be associated with various cancers), as well as anti-tumour promoting activity. Taraxasterol, was particularly active in these tests for anti-cancer activity.

More recent work by Korean researchers revealed potent antiproliferative activity by taraxinic acid, a sesquiterpene lactone found in various species of Taraxacum, against human leukaemia cell lines[5]. In vitro antioxidant and cytotoxic activity (at least partly attributable to luteolin) has also been documented for extracts of dandelion flowers[6].

These studies were extended to measure the effects of dandelion extracts on human liver cancer (hepatoma) cells in vitro, in a recent study whose results were published in the journal Life Science[1]. This work has confirmed earlier findings of cytotoxic properties on cancerous cells for dandelion extract, and related this activity to influences on production of various cytokines in these cell lines. These included an increase in tumour necrosis factor (TNF)-alpha and interleukin–1alpha production, effects which were shown in this study to contribute to dandelion-induced cytotoxicity in hepatoma cell lines.

While only a laboratory study, these results suggest that indications for the use dandelion root could perhaps be extended to include potential benefits in the prevention or treatment of liver cancer in humans.

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Milk Thistle for Prostate Cancer?

Milk thistle (*Silybum marianum*) has shown promise as an anticancer agent in several scientific studies conducted in recent years, including colon, tongue and liver cancer as well as leukaemia[1,2,3,4].

The high rate of prostate cancer in male populations, and difficulties in treating this slow growing but life threatening cancer with conventional medicine, has lead to a search for alternative treatment agents by researchers around the world. Silibinin, a major active flavonoid component of the flavonolignan complex silymarin found in milk thistle seeds, as well as silymarin itself, has produced significant inhibition of the growth of prostate cancer cell lines *in vitro*[5].

Researchers at the Department of Urology, Georg-August University in Gottingen, Germany, have extended these investigations to evaluate the effects of silibinin on the expression of prostate specific antigen (PSA) mRNA and PSA secretion, using a conditioned medium under basal and 5-alpha-dihydrotestosterone (DHT) simulated conditions[6]. DHA was shown to stimulate both prostate epithelium-derived Ets transcription factor (PDEF) and PSA gene expression, and consequently PSA secretion. The treatment of these prostate cancer cell lines with silibinin resulted in down-regulation of basal as well as DHT stimulated PDEF and PSA, demonstrating the antiproliferative potential of this milk thistle constituent. The authors conclude that these effects underline the possible therapeutic use of silibinin in the management of prostate cancer.

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Dietary supplementation compared to Ritalin® for ADHD

Attention-deficit/hyperactivity disorder (ADHD) occurs in an estimated 3 to 10% of American children[1], and is sometimes associated with academic impairment, social dysfunction, and poor self-esteem. Evidence suggests that the overall rate of drug medication for ADHD has been increasing, with more than 2 million American children being treated with stimulants in 1997[1]. Controversies exist with this treatment, due to its possible association with drug use later in life[2], an increased occurrence of psychotic symptoms[3], and disruption of growth hormone production resulting in growth suppression[2]. In addition to this, an estimated 30% of children with ADHD either do not respond to drug treatment, or find side effects unmanageable. Alternative treatments such as diet, iron supplementation, neurofeedback and herbal remedies, have therefore become more popular in recent years.

In a study published by American researchers late last year, twenty children with Attention deficit/hyperactivity disorder were treated with either methylphenidate (Ritalin®) or dietary supplements and were assessed using various performance tests[4]. Researchers reported an essentially identical improvement in performance in both groups on all tests. The dietary supplements used consisted of a mix of vitamins, minerals, phytonutrients, amino acids, essential fatty acids, phospholipids, and probiotics.

The researchers concluded that their findings support the effectiveness of food supplement treatment in improving attention and self-control in children with AD/HD and suggest food supplement treatment of AD/HD may be of equal efficacy to Ritalin® treatment.

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Obesity predisposes to Alzheimers disease

Nutritional factors have been implicated in the aetiology of Alzheimer's disease (AD) since the first studies reporting higher levels of aluminium in the brains of Alzheimers patients, were published in 1975[1]. Since that time various studies have looked at the possible influences of environmental factors such as diet, aluminium, exercise and viruses on the development of AD. Protection against AD and dementia has how been found for various dietary factors, including a high intake of flavonoids and vegetables[2,3,4], fish and cereals[5,6], and monosaturated fatty acids[5].

Interest in the potential role of dietary lipids in the pathophysiology of AD began to increase in the late 1990's[7]. Various biochemical and cell biological studies now suggest that altered cholesterol metabolism in neurons may contribute to the development of the disease[8], and results of some epidemiological studies support this. These include an American study where 980 elderly individuals free of dementia were followed for a mean of 4 years, which found that individuals with the highest intake of calories had a 50% higher risk than those with the lowest calorific intake of developing AD[9]. When these results were matched against the presence of the apolipoprotein E epsilon4 allele, a known genetic risk factor for AD, this risk in those consuming a high calorie diet was found to be 2.3 times that of individuals who lacked this gene. The risks of AD in those who lacked this gene but consumed a high calorie diet, was subsequently reported to be the same as in those who lacked the gene but ate a low calorie diet, which would seem to reinforce the major contribution of the presence of this genetic risk factor . It is likely however, that non-genetic risk factors are also strongly contributory to the aetiology of AD, due to the marked alterations in its occurrence following migration, the lack of spatial uniformity of age-related death rates from it, and the increased incidence over time[10].

Further evidence that cellular cholesterol homoeostasis is involved in the pathophysiology of AD, derives from studies into the processing of the nerve protein amyloid beta-peptide precursor protein (APP). Abnormal APP breakdown has been linked to the development of AD and this breakdown is modulated by cholesterol lowering drugs which produce changes in cellular cholesterol levels[11]. Some evidence that the use of cholesterol lowering statin drugs may reduce the incidence of AD, has also been reported by recent retrospective epidemiological studies[12].

Weight loss is commonly seen in patients following development of AD, despite the fact that daily calorie intake usually remains the same as that of non AD patients[13]. It seems likely that the pathophysiological processes in AD lead to the changes of appetite and metabolic status in AD patients which contribute to this weight loss.

Women seem to have a higher risk of AD, as do people with lower levels of education; head injury, several occupational exposures, and exposure to aluminium in the water supply[14]. Hypertension, type 2 diabetes and other vascular symptoms appear to predispose to AD[15,16,17].

While several apparently protective factors have been identified, (use of NSAID drugs, oestrogen by post-menopausal women, physical exercise, dietary levels of vitamins B6, B12 and folate; red wine in moderate quantities), preventive trials based on these have to date failed to show much evidence of effectiveness[14].

Oxidative stress appears to be involved in cerebral aging and dementia[18]. Dietary intake of antioxidants has been proposed to protect against AD, although mixed findings from two recently published epidemiological studies have been reported. The first of these involving 4740 men and women aged 65 years or older found use of vitamin E and vitamin C supplements in combination but not alone to be associated with a reduced prevalence and incidence of AD over a 3 year period[19]. No such association with intakes of beta-carotene, flavonoids and vitamins E and C was however measured by another study involving 2459 men who were followed over a one to six year period, after adjusting for sociodemographic and lifestyle factors, cardiovascular risk factors, other dietary factors and apolipoprotein E e4[20]. While omega-3 polyunsaturated acid intake has been suggested to protect against the risk of dementia and AD, plasma levels of these and their metabolites were shown to be higher rather than lower, in patients with dementia in this study.

Based on all studies to date however, it would appear that dietary antioxidants and supplements and specific macronutrients of the diet may act synergistically with other protective factors, to reduce the prevalence of AD[5].

Results from a Swedish study where 392 nondemented people were followed over an 18 year period from the age of 70 to 88, have recently provided further insight into the possible contribution of weight as well as gender as risk factors for dementia, including AD[21]. Women who developed dementia during the 18 year follow-up period, were found to have a higher average BMI (basal mass index) compared with nondemented women, and the more overweight women were even more likely to develop AD. For every 1.0 increase in BMI at age 70 years, AD risk increased by 36%. These associations were not found in men. The authors concluded that being overweight in old age is a risk factor for dementia, particularly AD, in women.

Continued on page 14

Continued from page 13

Obesity and being overweight are now endemic problems in western societies, and media coverage of this issue has increased during the past 2 years. With the global aging of the human population, the occurrence of cognitive impairment and dementia is rapidly becoming a significant burden for medical care and public health systems[15]. Elimination of potential risk factors and implementation of possible protective factors should therefore be key objectives for all health professionals.

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Monsanto drops plans for drug production through genetically modified plants

Monsanto, the world's largest agricultural biotechnology company, has halted plans for producing drugs through genetically modified plants. The company cited "uncertainty of longer-term reward" as its reason for this step, as well as a decision to focus on more immediately profitable areas such as seeds and its leading product, the herbicide Roundup®[1].

Much criticism had been directed at Monsanto for its programme to develop pharmaceuticals through modifying the genes of plants, particularly for the fear that such modification could result in complete contamination of the modified species. Engineering agricultural corn to produce antibiotics for example, could eventually lead to the complete contamination of all commercially grown corn with antibiotics, which could be very dangerous not only to consumers but to the long-term viability of the products of commercial agriculture.

The process of plant vectoring, which involves insertion of new DNA sequences into plant genomes and causes the plant to express the new DNA's protein product, is not yet practiced commercially. A similar process involving animal or bacterial cells grown in controlled environments, is however now widely used in drug production. Many biotech scientists are pursuing the use of plant vectors as a cheaper and more efficient technique. Alarmingly, lobbying of organic agriculture representatives in India and African countries is now underway to accept the introduction of plants genetically modified to possess resistance to common plant pathogens as an alternative to herbicides or more labour-consuming organic management methods[2]. This combined with recent U.S. moves to broaden the definition of what constitutes an 'organically produced' plant or animal[3], highlight the growing threats to the availability of plants produced from their natural origins according to traditional organic methods.

The lack of knowledge by the American public on these issues was shown by a study conducted last year by the Food Policy Institute at Rutgers University in New Jersey. This revealed that only half of Americans knew that foods with genetically modified ingredients are sold in U.S. stores, and only 25% thought they had consumed modified foods at some point[4].

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Organic growing leads to more biodiversity

Organic farming has increased substantially during recent decades, catalysed by growing consumer concerns about the use of pesticides and herbicides in agriculture. This trend has been strongly resisted in some countries however, such as in the U.S. where only 0.28% of land under production is devoted to organic crops or animals, compared to 3.64% of agricultural land in Western Europe[1].

Apart from providing the food, fuel and fibre needs of the world's population, the soil regulates the quality of air and water, decomposes organic wastes and recycles nutrients, and acts as a sink for pollutants including global gases[2]. Soil fertility and nutrient content is a critical factor influencing the quality of food produced from it, as well as its requirement for additional external inputs, its susceptibility to degradation, and its ability to perform these other important functions.

A number of short-term studies support the notion of a healthier status including better fertility and biodiversity for land that has been organically managed, although relatively few well designed studies into the potential long-term benefits of organic farming have been conducted to date. Recent research undertaken by workers at the Botanical Institute in Basel, Switzerland, has however shown an improved health status for a type of soil fungi that play a vital role in nutrient acquisition and soil fertility, following long-term organic farming[3].

Arbuscular mycorrhizal fungi (AMF) play a crucial role in enabling the soil to acquire nutrients and optimise fertility, and the presence of a healthy population of such soil microorganisms is known to be associated with good soil health[2]. The relative number and diversity of AMF found in soil from replicated field plots which had been cultivated for 22 years according to two organic and two conventional farming systems, was measured by the Swiss team. Their findings were that the AMF spore abundance and species diversity was significantly higher in the land that had been cultivated organically than in the conventionally managed land. Several species of AMF which are normally present in natural ecosystems were shown to be maintained under organic farming, but were severely depressed under conventional farming.

These findings reinforce the benefits of long-term organic farming to the biodiversity of microorganisms which are important in maintaining soil health, and indicate a potentially severe loss of ecosystem function by long-term conventional farming.

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Positive recommendations from Ministerial Advisory Committee on Complementary & Alternative Health.

A major report into complementary and alternative medicine by the government appointed Ministerial Advisory Committee on Complementary and Alternative Health (MACCAH), was released in New Zealand on 3 August 2004. The report, the culmination of three years work by this committee to consider how better to recognise, regulate and integrate complementary health practitioners, forms the final advice of the committee to the Minister of Health, and makes many significant recommendations.

MACCAH released a discussion document in 2003, which formed the basis for nationwide consultation. A total of 315 written submissions were received from a wide range of complementary and alternative medicine (CAM) and orthodox health organizations, as well as individuals, training establishments and voluntary organizations.

The MACCAH report recommends that treatments proven to be safe, efficacious and cost effective should be publicly funded, and a unit established within the Ministry of Health to take steps to integrate complementary and mainstream healthcare. It recommends that all complementary health practitioners should be regulated according to the level of inherent risk involved in the modalities they practice, and that the process of regulating practitioners of high-risk modalities should continue under the Health Practitioners Competence Assurance Act.

The report also highlighted the need for more research on complementary and alternative medicine, and for research-funding bodies to be encouraged to facilitate further research on these medicines.

The National Health Committee is also organising a CAM summit for late this year to enable mainstream and CAM sector representatives to discuss opportunities to work together in the future.

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