PHYTOTHERAPY RESEARCH
*Phytother. Res.* **14**, 1–14 (2000)

*Review Article*

# The Chemistry and Biological Activity of Herbs Used in Flor-Essence™ Herbal Tonic and Essiac™

**Carmen Tamayo,[1] M. A. Richardson,[2]* Suzanne Diamond[3] and Inga Skoda[3]**

[1]Foresight Link Corporation, Ontario, Canada
[2]The UT Center for Alternative Medicine Research, Center for Health Promotion Research and Development, University of Texas, U.S.A.; Houston School of Public Health, Houston, Texas, U.S.A.
[3]Flora Manufacturing and Distributing Ltd, Burnaby, British Columbia, Canada

**The herbal mixtures, Essiac™ and Flor-Essence™, are sold as nutritional supplements and used by patients to treat chronic conditions, particularly cancer. Evidence of anticancer activity for the herbal teas is limited to anecdotal reports recorded for some 40 years in Canada. Individual case reports suggest that the tea improves quality of life, alleviates pain, and in some cases, impacts cancer progression among cancer patients. Experimental studies with individual herbs have shown evidence of biological activity including antioxidant, antioestrogenic, immunostimulant, antitumour, and antiocholeretic actions. However, research that demonstrates these positive effects in the experimental setting has not been translated to the clinical arena. Currently, no clinical studies of Essiac™ or Flor-essence™ are published, but a clinical study is being planned at the British Columbia Cancer Agency by the University of Texas-Center for Alternative Medicine (UT-CAM) and Tzu-Chi Institute for Complementary and Alternative Medicine.** **Copyright © 2000 John Wiley & Sons, Ltd.**

*Keywords:* Flor-Essence™; Essiac™; burdock (*Arctium lappa* L); red clover (*Trifolium pratense* L.); blessed thistle (*Cnicus benedictus* L.); slippery elm bark (*Ulmus rubra* Muhl.); sheep sorrel (*Rumex acetosella* L); Turkish rhubarb root (*Rheum palmatum* L.); kelp (*Laminaria digitata* Lmx.); watercress (*Nasturtium officinale* R. Br.); phytoestrogens; anthraquinones; emodin; anthracenes; glucosinolates; cancer treatment; traditional medicine; herbs.

## INTRODUCTION

Flor-Essence™ and Essiac™ are two of the most widely used herbal products by cancer patients at estimates of 35% in some Canadian populations (Gray *et al.*, 1997). Both products contain four principal herbs: Burdock root (*Arctium lappa* L.), Turkish rhubarb root (*Rheum palmatum* L.), sheep sorrel (*Rumex acetosella* L.) and slippery elm bark (*Ulmus rubra* Muhl.). However, the Flor-Essence™ blend has four additional herbs: watercress (*Nasturtium officinale* R. Br.), blessed thistle (*Cnicus benedictus* L.), red clover (*Trifolium pratense* L.) and kelp (*Laminaria digitata* Lmx.).

The Flor-essence™ formula is proprietary; however, the composition in descending order of magnitude is as follows: 1. burdock root, 2. sheep sorrel herb, 3. slippery elm bark, 4. watercress herb, 5. kelp, 6. blessed thistle herb, 7. red clover herb, 8. Turkish rhubarb root.

* Correspondence to: M. A. Richardson, The UT Center for Alternative Medicine Research and Center for Health Promotion Research and Development, University of Texas, Houston School of Public Health, PO Box 20186, Houston, Texas 77225, USA.
e-mail: marich@utsph.sph.uth.tmc.edu
Contract/grant sponsor: National Institutes of Health; Contract/grant number: 5 U24 CA66826-03.

CCC 0951–418X/2000/010001–14 $17.50
Copyright © 2000 John Wiley & Sons, Ltd.

The formula is attributed to Ojibwa Native American folklore and has been used for almost eight decades. In the early 1920s, a Canadian nurse, Rene Caisse, learned of the formula from a breast cancer survivor. This survivor had not received surgery or conventional treatment and attributed her cure to the tonic. She reportedly remained disease-free for 30 years. Caisse began using the formula and successfully treated her aunt and several other individuals who had cancer. Over time, this treatment became popular. Caisse reduced the formula to what she considered the most important ingredients: burdock root, rhubarb root, slippery elm bark, and sheep sorrel and named it Essiac™, which was her last name spelled backwards. She subsequently worked with Dr Charles Brusch, the famous physician of President Kennedy, to improve the formula and returned to an eight-herb formula. That formula is available in health food stores as Flor-Essence™ (Fraser and Allen, 1977; Thomas, 1993).

The formula was promoted as a detoxificant and stimulatory agent. The tonic has been marketed for over 20 years, and anecdotal reports suggest the formula improves quality of life and prolongs survival, but no claims as a cancer cure have been confirmed (Canadian Breast Cancer Research Initiative, 1996). Although each herb in the formula has not been evaluated for anticancer activity, each contains specific biological activity. The

*Received 16 April 1999*
*Revised 16 August 1999*
*Accepted 24 September 1999*

formula has been shown to have strong antioxidant action and contains trace elements, minerals, and phytoestrogens (Flora Manufacturing and Distributing Ltd, 1996 unpublished data).

Combined sales of Essiac™ type products are beyond $8 million annually, based on liquid and dry herbs for wholesale and mail order customers. Sales of Flor-Essence™, marketed by Flora Manufacturing and Distributing Ltd are estimated at $4.5 million with 40 000 bottles and an additional 40 000 packages of dried herbs shipped monthly to the USA and Canada. The Essiac™ product by Resperin Corporation has estimated sales of approximately $3.2 million per year (The University of Texas-Houston Center for Alternative Medicine, 1998).

## CURRENT RESEARCH

A literature review conducted by the University of Texas Center for Alternative Medicine Research (UT-CAM) identified 107 references on the four principal herbs used in both preparations, of which 73 (68%) were applicable to cancer. Although testimonials are reported, no clinical trials have been completed. UT-CAM identified 13 *in vivo* and 11 *in vitro* evaluations of individual herbs, but none on the tonic itself (The University of Texas-Houston Center for Alternative Medicine, 1998). However, Flora Manufacturing and Distributing Ltd has initiated preclinical and clinical evaluations of Flor-Essence™ in Russia with the Russian Ministry of Health, who are interested in using Flor-Essence™ to treat victims of Chernobyl. Preclinical pharmacology trials with several different animal species have documented (Flora Manufacturing and Distributing Files, 1997) that Flor-Essence™ possesses: (1) immunostimulatory activity by increasing the ability of mice to respond to immunologic challenge and increasing serum antibody titres; (2) immunomodulatory activity determined by increased phagocytic activity of macrophages and functional activity of phagocytes; (3) adaptogenic activity by increasing the endurance of mice subjected to a physical task; (4) antitoxic, gastroprotective, hepatoprotective and antihypoxic activity by providing a clear degree of protection against the hepatotoxicity induced by administration of carbon tetrachloride. Flor-essence™ reduced the number and relative size of chemical mediated gastric ulceration in rats; (5) capillary-protective effects in xylene-mediated capillary leakage, and (6) antiinflammation that is chemically induced. In addition, Flor-Essence™ was found to preserve homeostasis by enhancing natriuresis without changing potassium ion excretion in rats. Acute toxicity of Flor-essence™ herbal blend was determined on albino mice and rats. The test preparation was administered orally once or twice (with a 20–30 min interval) in various doses and volumes. Animal behaviour, appearance, and reaction to environmental factors were monitored for 14 days. No animal died during the experiments. Chronic toxicity was also determined in rats. The animals were divided in two groups. The rats of group I ($n = 15$) received daily for 5 days/week a 10-fold therapeutic dose (15 mL/kg orally) of the preparation for 3 months. The control group ($n = 15$) received the same volume of water. General physical condition, peripheral blood and biochemical parameters to evaluate renal and hepatic toxicity were recorded. Pathomorphological examination of internal organs was done at the end of the experiments. The tonic had no toxic effects at 10-fold maximum therapeutic dose and there was no toxic alteration on internal organs. A 3-month chronic toxicity study was also conducted in dogs receiving a 5-fold therapeutic dose (7.5 mL/kg) 5 times a week for 3 months. All dogs appeared to be in good health for the duration of the treatment period and no major pathological changes were noted (Flora Manufacturing and Distributing Files, 1997).

Clinical trials with Flor-Essence™ conducted by the Ministry of Health of the Russian Federation at the Moscow Regional Research Clinical Institute (Gastroenterology Department) concluded that Flor-Essence™ is an effective treatment for chronic gastrointestinal diseases. They recommend the tonic as the basic treatment for chronic non-healing erosions of the gastric mucosa (i.e. catarrhal oesophagitis, erosive-ulcerous oesophagitis, candidal oesophagitis, chronic gastritis, haemorrhagic gastritis, post-gastrectomy syndrome, duodenitis, duodenal ulcers, chronic colitis, and cirrhosis of the liver). The preparation is well tolerated and recommended for use in clinical practice for the complex treatment of gastrointestinal diseases. When comparing the dynamics of subjective and objective parameters among patients taking Flor-Essence™ ($n = 35$) with a control group ($n = 36$), more rapid and marked improvement of dyspeptic symptoms was observed in patients treated with Flor-Essence™. There was a 52% reduction in number of complaints in the Flor-Essence™ group compared with a 37% in the control group. The average duration of dyspeptic symptoms of all kinds was 6.4 days in the main group versus 9.6 days in the control group. The differences were statistically significant. The tonic also exhibited a minor immunomodulatory effect and exerted a positive therapeutic effect in patients with secondary immune deficiency (Itigina *et al.*, 1998 unpublished data; Flora Manufacturing and Distributing Files, 1997).

Flora Manufacturing and Distributing, Ltd also is collaborating with UT-CAM to characterize the product, standardize the tonic, and develop a clinical trial to evaluate the safety and feasibility of testing in a cancer population. UT-CAM is also conducting an epidemiological study to document the pattern of use of Flor-Essence™ herbal tonic in North America and gathering detailed information on use and perceived benefits by cancer patients. In Russia, clinical trials with Flor-Essence™ as a cancer treatment are ongoing at the Moscow Regional Research Clinical Institute.

## REVIEW OF RESEARCH

Recent medical research poses possible mechanisms of action of the Flor-Essence™ formula as an anticancer agent. Biochemical analyses have demonstrated that the tonic contains several phyto- or plant oestrogens. Both the liquid and dry herbal blend have been tested and found to have oestrogen receptor binding activity and slight progesterone receptor binding activity (Zava and Duwe, 1997). Most of the evidence is based on *in vitro* studies, however, few *in vivo* studies are reported and no clinical trials in the United States or Canada with the whole tonic have been conducted to date; however,

Copyright © 2000 John Wiley & Sons, Ltd. 

preclinical and clinical trials on gastroenterology patients have been conducted by the Russian Ministry. Articles addressing the beneficial antimutagenic, anticarcinogenic, and antioxidant effects of several of the herbs have been published (Silver and Krantz, 1931; Ley and Reeve, 1997; Yang *et al.*, 1997; Odin, 1997; Agarwal and Mukhtar, 1996; Dombradi and Foldeak, 1996; Foldeak and Dombradi, 1964; Morita *et al.*, 1984, 1985; Kimura *et al.*, 1980; Maruta *et al.*, 1995). Thus, the herbal mixture may have synergistic antitumour and immunostimulant activities since the individual herbs exhibit specific biological activity.

A summary of the most recent experimental and clinical data on each of the eight herbs is provided below. The summary includes information on the composition of each herb and a review of the proposed mechanisms of action.

## Burdock (*Arctium lappa* L.)

**Composition.** The root contains at least five powerful flavonoid-type antioxidants (i.e. caffeoylquinic acid derivatives) and several polyphenols that are more powerful antioxidants than vitamin C (Maruta *et al.*, 1995). The seed contains platelet activating factor (PAF) inhibitors (Iwakami *et al.*, 1992) that may reduce symptoms of PAF related diseases, such as arthritis and asthma. As much as 75% of the carbohydrate content in the plant is stored in the root as a complex fructan, gamma-glucoside-fructose ester, known as inulin (Harborne and Herbert, 1993). Burdock seed also contains polyacetylenes (Takasugi *et al.*, 1987) that have antibacterial, antifungal and anti-HIV activity (World Health Organization, 1989; Yao *et al.*, 1992; Takasugi *et al.*, 1987) and tannins.

**Mechanisms of action.** (a) *Protection against cellular damage and anticancer activity: In vitro* studies demonstrated that the aqueous extract of burdock root decreased mutations in cells exposed to toxic chemicals (Morita *et al.*, 1984). In addition, animals that consumed burdock root were protected against several toxic chemicals (Kimura *et al.*, 1980; Dombradi and Foldeak, 1966; Foldeak and Dombradi, 1964; Morita *et al.*, 1985). The anticarcinogenic activity of natural and synthetic flavonoids has been evaluated in mice. Administration of the synthetic flavone B-naphthoflavone resulted in an almost total inhibition of pulmonary adenoma formation induced by benzo(*a*)pyrene. Quercetin, a natural flavone found in burdock produced a 50% inhibition (Wattenberg and Leong, 1970). Isoflavone derivatives such as genistein and biochanin A, nobiletin and tangeretin, which are naturally occurring flavones in burdock root, have been shown to induce apoptosis of tumour cells and cytostatic effects in cell lines. *In vivo* isoflavones suppressed the tumour growth of cell lines in nude mice (Yanagihara *et al.*, 1993). The tannins in burdock also induce macrophage response and act as immunomodulators; in certain tumour cells in mice, they exhibit strong antitumour effect (Miyamoto *et al.*, 1993).

(b) *Cellular differentiation and anticancer activity*: Differentiation-inducing activity of over 180 extracts of crude drugs and plants were tested using a mouse myeloid leukaemia cell line(M1) (Umehara *et al.*, 1992). Lignoids from the fruit (*Arctium fructus*), rather than the root of *Arctium lappa* L, have been investigated against undifferentiated mouse myeloid leukaemia cells (M1) and found to induce more than half of the M1 cells into phagocytic cells at a concentration of 2μM after 24 h treatment with this extract. The active components of this extract, the dilignans, have been isolated; the most active lignan identified is arctigenin 1 and its aliphatic ester *n*-decanoate (Umehara *et al.*, 1996). The lignans arctiin and its aglycone, arctigenin are also noted for anticancer activity (Duke, 1992b; Vanhaelen and Vanhaelen-Fastre, 1975). These lignans have been shown to have potent *in vitro* cytotoxic activity and *in vivo* antitumour activity against human hepatoma HepG2 cells and mouse sarcoma 180 cells (Moritani *et al.*, 1996).

(c) *Modification of intestinal microflora by inulin*: A clinical study found that an increased intake of oligofructose and inulin significantly increased bifidobacteria and decreased numbers of potential pathogens (Gibson *et al.*, 1995). An increase in oligosaccharides was reported to lead to a selective qualitative change in caeco-colonic microbial flora (i.e. bifidogenisic change) (Roberfroid, 1993; Gibson *et al.*, 1995). Inulin is not digested in the stomach but fermented almost exclusively by colonic bifidobacteria and bacteroides. The complete fermentation increases faecal bacterial biomass, decreases colonic pH, and increases fermentation products such as short chain fatty acids that positively affect the metabolism of lipids (Jensen *et al.*, 1997; Hidaka *et al.*, 1986; Kies, 1985; Hoverstad and Bjorneklett, 1984). Beneficial intestinal bacteria have been found to stimulate the immune system and effectively suppress tumour cells (Fernandes and Shahani, 1990; Shahani *et al.*, 1989).

(d) *Antiinflammatory and free radical scavenger activity*: Subcutaneous administration of a crude extract of *A. lappa* significantly decreased carrageenan-induced rat paw oedema. The extract also reduced hepatotoxicity induced by the toxic substance, carbon tetrachloride. The research suggests that *Arctium lappa* possesses free radical scavenging activity and strong antioxidant activity (Lin *et al.*, 1996; Duh, 1998).

(e) *Antidiabetic properties*: The hydrolytic product of inulin is fructose, a more labile monosaccharide than glucose (Silver and Krantz, 1931). The high levels of inulin in burdock root and its water extract, provide a natural carbohydrate that helps to keep blood sugar levels constant (Silver and Krantz, 1931). Older studies suggest that inulin has the ability to lower hyperglycaemia, and the mechanism is thought to be due to the action of inulin on the reserve of insulin and internal secretions of the pancreas (Root and Banker, 1925; Yamashita *et al.*, 1984; Luo *et al.*, 1996). Although inulin is an indigestible carbohydrate, no recent data suggest that inulin ingestion would interfere with diabetes aetiology or control. Nevertheless inulins are mostly linear polymers of fructose with glucose as a terminal sugar, and they are considered a type of soluble-viscous-fermentable fibre that may help control glucose levels in several ways. Inulin has been shown to: (a) improve bowel habits; (b) improve stool composition; (c) decrease intestinal transit time; (d) improve glucose tolerance; (e) reduce glucose and starch absorption; (f) reduce intraluminal pH; (g) change the composition of caeco-colonic microbial flora towards a potentially healthier bifidobacteria microflora; (h) increase the production of short chain fatty acids and; (i) reduce blood cholesterol (Gibson *et al.*, 1995).

Copyright © 2000 John Wiley & Sons, Ltd. 

**Red clover herb (*Trifolium pratense* L.)**

**Composition.** Red clover is a legume that contains large amounts of the phytoestrogen genistein (Franke *et al.*, 1994). Phytoestrogens are recognized as agents for cancer prevention and treatment (Kelloff *et al.*, 1996; Hirano *et al.*, 1994; Cassady *et al.*, 1988; Wahlquist and Dalais, 1997; Slavin *et al.*, 1997; Clarke *et al.*, 1996; Morton *et al.*, 1997a). Specifically, genistein is considered the active compound in soy. Chemical analysis and biological studies of the phytoestrogen content of legume plants, including red clover, white clover, alfalfa, soy, liquorice and goat's rue (*Galega officinalis*) indicate that red clover contains four beneficial oestrogenic isoflavones: genistein, daidzein, formononetin and biochanin-A (Sachse, 1974). Research on dietary legumes, indicates that phytoestrogens are necessary for a balanced diet and beneficial for health promotion and disease prevention (Zava, 1998, personal communication; Potter and Steinmetz, 1996). The phytoestrogen content varies from 1.0% to 2.5% of dry matter (Saloniemi *et al.*, 1995; Kurzer and Xu, 1997).

**Mechanism of action.** (a) *Inhibition of excess endogenous human oestrogen synthesis*: Among the soy products, genistein is recognized as critical for preventing many modern hormone related diseases in men and women, including menopausal symptoms, osteoporosis, cancer and heart disease (Kurzer and Xu, 1997; Miksicek, 1993; Barnes *et al.*, 1994; Kao and P'eng, 1995; Draper *et al.*, 1997; Anderson and Garner, 1997). Studies have shown a correlation between high levels of urinary lignans and isoflavonoid phytoestrogens, particularly genistein, and a low incidence of hormone-dependent cancers, such as breast and prostate cancer (Mousavi and Adlercreutz, 1993). The mechanisms are thought to involve oestrogen metabolism and bioactivity. In *in vitro* studies genistein and daidzein inhibit the growth of both oestrogen receptor-negative and -positive human breast cancer cell lines ($IC_{50}$ = 24–44 μM) (Peterson and Barnes, 1993) and inhibit DNA topoisomerase activities (Traganos *et al.*, 1992). Phytoestrogens in the diet dilute xenoestrogen-type carcinogens by binding at receptor sites and function as antioestrogen drugs. They affect the enterohepatic circulation of oestrogens by reducing circulating blood levels of oestradiol (Rose, 1992). The phytoestrogens, genistein and daidzein, tend to normalize oestrogen and progesterone (Zava *et al.*, 1997, 1998; Zava and Duwe, 1997). In controlled experiments with ovariectomized ewes, clinically significant changes in oestrogenic activity occurred in the reproductive organs of animals that ate red clover. These changes were similar, but more pronounced during treatment with 17 beta-oestradiol (Nwannenna *et al.*, 1995).

(b) *Anticancer activity*: *In vitro* tests of phytoestrogens have shown that genistein inhibits endothelial cell proliferation, *in vitro* angiogenesis, and proliferation of tumour cells (Barnes, 1995; Fotsis *et al.*, 1995; Peterson and Barnes, 1993). Genistein inhibits the vascularization of the cancer (Barnes *et al.*, 1990). When the urine of healthy human subjects consuming a plant-based diet was examined, one of the most potent fractions that inhibited vascular endothelial cells proliferation contained isoflavonoids. Genistein was the most potent and inhibited *in vitro* angiogenesis and the proliferation of various tumour cells. Therefore, researchers concluded that a plant-based diet helps prevent solid tumours by inhibiting neovascularization and tumour cell proliferation (Fotsis *et al.*, 1995). Two-thirds of studies in animal models found that the cancer risk (i.e. incidence, latency or tumour number) was significantly reduced with genistein-containing soy materials. In addition, purified genistein delayed the incidence of mammary tumours *in vivo*, and *in vitro* studies showed that genistein inhibited the proliferation of human tumour cell lines at concentrations similar to that of individuals consuming a plant-based diet (Barnes, 1995).

(c) *Antioxidant and cellular differentiation activity*: Genistein is a powerful antioxidant with cellular differentiation activity (Kurzer and Xu, 1997). Differentiation is achieved by stabilizing protein-linked DNA strand-breakage or dynamic changes in chromatin structure. Genistein acts by inhibiting C-ABL tyrosine kinase activity, allows normal cell differentiation and inhibits phosphorylation and dephosphorylation. The ultimate effect is a dose-dependent inhibition of cell multiplication and induction of cell differentiation (Constantinou and Huberman, 1995; Barnes and Peterson, 1995; Lamartiniere *et al.*, 1998).

(d) *Detoxification*: Red clover tea is recognized traditionally for facilitating the elimination of wastes and toxins through the kidneys, skin and bowels. This herb also increases the activity of phagocytes, the scavenger cells of the immune system that remove microorganisms and debris from blood and mucus (Duke, 1989, 1990; Derwick, 1977).

(e) *Antibacterial*: Research has shown that red clover contains antimicrobial compounds that are effective against several bacterial, viral and fungal infections (Shar, 1993). The four main phytoestrogens in red clover are well established antimicrobial agents. In addition, biochanin A, formononetin and genistein are effective fungicides at low concentrations (Duke, 1992a).

**Epidemiological studies.** A great deal of evidence supports the hypothesis that adequate dietary lignan and isoflavone intakes reduce cancer risk (Barnes *et al.*, 1990, 1994; Setchell and Adlercreutz, 1988). Several papers have reviewed the potential roles of phytoestrogens present in red clover and other legumes in preventing breast, colon and prostate cancer (Barnes and Peterson, 1995; Barnes, 1995; Messina *et al.*, 1994).

In China, two legumes have been used for centuries to treat breast cancer: soybeans and liquorice root. A number of epidemiological studies have shown that Japanese women who consume a high soy diet have one-fifth the rate of breast cancer compared with women who do not eat soy; the protective effect is attributed to genistein (Lee *et al.*, 1991; Lee, 1991; Kennedy, 1995). Red clover contains approximately 2% of phytoestrogens based on dry weight—said to be *10 times more than* is found in soy (Aykroyd and Doughty, 1982; Reinli and Block, 1996; Kelly *et al.*; Biggs and Lane, 1978). The lower risk of breast, colon and prostate cancer in populations from Asia compared with American and Western European countries has resulted in studies of the role of dietary phytoestrogens (American Cancer Society, 1993; Goodman *et al.*, 1997; Herman *et al.*, 1995; Knight and Eden, 1995; Greenwald, 1989; Murkies, 1998; Stephens, 1997a). A high dietary intake of phytoestrogens is associated with a substantial reduction in risk for breast (Ingram *et al.*, 1997), endometrial (Goodman *et*

Copyright © 2000 John Wiley & Sons, Ltd. 

*al.*, 1997) prostate (Stephens, 1997b; Morton *et al.*, 1997b) and salivary gland (Horn-Ross *et al.*, 1997) cancer. A case–control study of 144 women with recently diagnosed breast cancer found a substantial reduction in breast-cancer among women with a high intake of phytooestrogens—particularly the isoflavonic phyto-oestrogen equol and the lignan enterolactone (Ingram *et al.*, 1997).

### Blessed thistle (*Cnicus benedictus L.*)

**Composition.** The primary active ingredient of blessed thistle is a bitter-tasting compound called cnicin, a sesquiterpene lactone. The seed contains several lignans that are phytoestrogen precursors for the key mammalian lignans: enterolactone and enterodiol which are present in humans and animals (Stitch *et al.*, 1980; Rickard *et al.*, 1998). Cnicin aids digestion and has considerable antitumour, cytotoxic, antimicrobial and phytotoxic activity (Duke, 1992a; Rodriguez *et al.*, 1976).

**Mechanism of action.** (a) *Anticancer and cytotoxic activity*: Research on blessed thistle has demonstrated that cnicin has cytotoxic properties (Vanhaelen-Fastre and Vanhaelen, 1976). The lignans arctiin and its aglycone, arctigenin are also noted for anticancer activity (Duke, 1992b; Vanhaelen and Vanhaelen-Fastre, 1975). These two lignans are the same lignans that are found in burdock seed (*Arctium lappa* L.) and have been shown to have potent *in vitro* cytotoxic activity and *in vivo* antitumour activity against human hepatoma HepG2 cells and mouse sarcoma 180 cells (Moritani *et al.*, 1996).

(b) *Antibiotic activity*: Blessed thistle extracts have antibacterial activity (Vanhaelen-Fastre and Vanhaelen, 1976). Research on blessed thistle herb has demonstrated antibiotic properties for: (1) cnicin (Vanhaelen-Fastre and Vanhaelen, 1976), (2) the essential oil which includes n-paraffin (C-9–C-13), aromatic aldehydes (cinnamaldehyde, benzaldehyde, cuminaldehyde) and monoterpenes (citronellol, fenchone, p-cymene and others) (Vanhaelen-Fastre, 1973), and (3) the polyacetylenes (Vanhaelen-Fastre, 1974) contained in the herb. The essential oil has bacteriostatic action against *Staphylococcus aureus, S. faecalis*, but not *E. coli* (Vanhaelen-Fastre, 1974; Risch *et al.*, 1988).

(c) *Choleretic and hypolipidaemic action*: Through its bitter properties, blessed thistle increases the flow of gastric juices relieving dyspepsia, indigestion and headaches associated with liver congestion (Bradley, 1992a). British and German Pharmacopoeias recognize that 'bitters', including blessed thistle, stimulate bile flow and cleanse the liver (Blumenthal, 1998). Bitter compounds and commercial anticholesterolaemic drugs such as cholestyramine and colestipol promote bile acid excretion and conversion of cholesterol to bile acids (Kraft, 1997; Hardman and Limbird, 1996). In Europe 'bitter vegetable drugs' are considered medicinal agents and used to stimulate appetite, aid digestion and promote health (Weiss, 1988; Saunders, 1994). Studies confirm that bitters increase gastric juice and bile acid secretions by increasing the flow of saliva through stimulation of specific receptors on the mucus membrane lining of the mouth (Schneider and Lachner, 1987; Sticher, 1997; Blumberger and Glatzel, 1996)

(d) *Tonifying*: Traditionally in most countries, including England, Germany, Russia, China, India and Africa, bitters are used to strengthen and tonify the body (Flynn and Roest, 1995; Iwu, 1993; Reynolds and Martindale, 1993; European Scientific Cooperative on Phytotherapy, 1997). Certain bitter compounds found in the leaves, stems and barks of many plants such as the oligomeric proanthocyanidins concentrated in pine bark and grape seed, have been shown to improve blood circulation by binding to the membranes of blood vessels and capillaries, repairing collagen and elastin and preventing their degradation by enzymes and free radicals, thereby strengthening the vascular system (Facino *et al.*, 1994; Pizzorno, 1993).

(e) *Antiinflammatory action*: Cnicin has antinflammatory activity similar to that of indomethacin in the rat paw oedema screen (Schneider and Lachner, 1987; Vanhaelen-Fastre and Vanhaelen, 1976).

(f) *Anti-HIV and anti-PAF activity of seed lignans*: Studies have documented two lignans present in blessed thistle with anti-HIV activity: arctiin and artigenin (Schroder *et al.*, 1990). The lignans are platelet activating factor (PAF) antagonists as well (Iwakami *et al.*, 1992).

### Slippery elm bark (*Ulmus rubra* Muhl.)

**Composition.** The inner bark is very rich in mucilage, a complex mixture of polysaccharides including pentoses, methylpentoses and hexoses which form a soothing gelatinous fibre upon hydration (Beveridge *et al.*, 1969, 1971). After hydrolysis these polysaccharides give galactose and traces of glucose and fructose. The bark also contains high concentrations of antioxidants including beta-sitosterol, traces of beta-carotene and tannins including proanthocyanidins (Duke, 1992a). Oleic and palmitic acid are the major types of fatty acids present in this herb.

**Mechanism of action.** Slippery elm bark and root have been used as folk remedies for treating cancer and other conditions (i.e. abscesses, dysentery, urinary and kidney inflammations, fever, throat irritation, lung disturbances) (Hutchens, 1973). Poultices were used to treat rheumatism and gout, swollen glands and to arrest the spread of gangrene (Duke, 1985d).

(a) *Antiinflammatory and demulcent action*: The mucilage of slippery elm bark resists hydrolysis primarily by the stomach acids and enzymes; therefore, it acts as a demulcent and emollient to the digestive system and soothes the throat, nasal passages and lungs (Bradley, 1992b). The bark is recommended for cancerous or ulcerated stomach (Duke, 1985d).

(b) *Antioxidant properties*: The bark contains large concentrations of antioxidants (Duke, 1985d, 1992a; Stitt, 1990).

(c) *Antitumour activity*: Fatty acid esters such as oleic and palmitic acid have been tested for antitumour activity using ascitic tumour cells of Ehrlich carcinoma in mice. Although slippery elm fatty acids have not been tested directly, research has shown that fatty acids and monoglycerides induce cell death in the tumour cells (Kato *et al.*, 1971). The bark's viscous fibre has several direct and indirect anticancer effects: (1) reduces bowel transit time; (2) absorbs toxins from the bowel; (3) increases faecal bulk and dilutes stool materials thereby reducing stool contact with the intestinal mucosa; and (4)

Copyright © 2000 John Wiley & Sons, Ltd. 

enhances beneficial colonic bacteria and provides an excellent substrate for bacterial fermentation (Pedersen, 1987).

### Sheep sorrel (*Rumex acetosella L*)

**Composition.** At least ten native tribes of Canada and the United States have used this plant as a food and medicine (Turner and Kuhnlein, 1991). Sheep sorrel dried aerial parts contain rutin (0.53%), flavone glycosides (i.e. hyperoside or quercitin-3d-galactoside) 0.05%, and hyperin (12 mg/10 g) (Duke, 1992a; Thomas, 1993). Sorrel contains vitamin C, A, B complex, D, E, K, P and U. Several key trace elements and minerals are abundant in the herb, including: calcium, iron, magnesium, silicon, sulphur, copper, iodine, manganese and zinc (Thomas, 1993). Total vitamin C of the leaves varies from 750–1200 mg/100 g based on dry weight. The ash (8.1%) contains, in the oxide form, 20.0% calcium; 13.9% phosphorus; 13.4% magnesium; 28.3% potassium and 11.5% silicon (Wealth of India, 1991; Duke, 1992a). The leaves and stems contain beneficial carotenoids, chlorophyll and organic acids (i.e. malic, oxalic, tannic, tartaric and citric). The plant contains anthraquinones, which are a class of chemicals used as drugs including emodin, aloe emodin, chrysophanol, rhein and physcion (Fairbairn and Muhtadi, 1972; Duke, 1992a). Emodin and the other anthraquinones have therapeutic benefits including anti-inflammatory, antiseptic, antispasmodic, antitumour, antiulcer, cathartic, cytotoxic, immunosuppressive; vasorelaxant and viricidal effects (Duke, 1992a, 1985b). Sheep sorrel also contains significant levels of phytoestrogens with notable oestrogen receptor binding activity (Zava *et al.*, 1998).

**Mechanism of action.** Sheep sorrel is a popular ingredient of many folk cancer remedies and has been used traditionally to treat fevers, inflammation and scurvy (Foster and Duke, 1990).

(a) *Antiinflammatory*: A tea of sheep sorrel was traditionally used as an antiinflammatory and diuretic agent (Foster and Duke, 1990).

(b) *Antioxidant and anticancer*: The aloe anthraquinone, emodin, has a number of therapeutic possibilities, including anticancer and cytotoxic activity (Duke, 1985b). Several anthraquinones including emodin, rhein, alizarin and aloe emodin are effective antioxidants and radical scavengers *in vivo* (Malterud *et al.*, 1993). The leaves of sheep sorrel are reported to be useful in treating cancer (Wealth of India, 1991).

(c) *Antibacterial*: Although research is limited on this species, a closely related species contains a powerful antibacterial compound called rumicin, which is effective against *Escherichia, Salmonella* and *Staphylococcus* (Duke, 1985b). *Rumex crispus* has been used traditionally to treat anaemia, anthrax, cancer, diarrhoea, eczema, fever, itch, leprosy, malaria rheumatism, ringworm, syphilis and tuberculosis (Duke, 1985b). A comparison of the distribution of anthraquinones (aglycones, O- and C-glycosides) in all parts of the plant of 19 representative species of *Rumex* showed an identical profile between *Rumex acetosa* and *Rumex acetosella* (Fairbairn and Muhtadi, 1972). Both plants contain aloe-emodin in the root and seeds and rhein compounds in the roots.

(d) *Laxative effect*: At low doses, most *Rumex* species are useful for treating diarrhoea; however, at higher doses, they are mild laxatives due to the presence of anthraquinones, that directly effect the neuromuscular tissue and stimulate peristalsis. At higher dosages, the anthraquinones increase the mucus production of colonic mucosa cells and stimulate secretion of water into the intestinal lumen, thereby exerting a laxative effect (Yagi *et al.*, 1997). The high content of tannins also can provide astringent action, which is useful for treating diarrhoea and excessive menstrual bleeding (Vanhaelen-Fastre, 1973; Foster and Duke, 1990; Hutchens, 1973).

### Turkish rhubarb root (*Rheum palmatum* L.)

**Composition.** Anthraquinones are the active ingredient in the root, including chrysophanol, emodin, aloe-emodin, rhein, physcionin, citreorosein, chrysophanol 1, emodin 1, aloe-emodin 8-glucoside; dianthraquinones: sennosides A, B, C, D, E and F; naphtalins, stilbenes and several polyphenols (Bradley, 1992b). Emodin at different concentrations has many therapeutic benefits including: antiinflammatory at 15 mg/kg; antiseptic; antispasmodic; antitumour; antiulcer, cathartic; cytotoxic with a $CD_{50}$ of 2.6 μg/mL; immunosuppressive; vasorelaxant and viricidal (Duke, 1992a, 1985b, 1985a). The root also contains a high tannin content.

**Mechanism of action.** (a) Remedy for digestive ailments: Turkish rhubarb root has been used traditionally to improve both digestion and loss of appetite (Duke, 1985c). The bitter root tea increases the flow of saliva and gastric secretions and functions as a safe and effective laxative. The plant is a component of many choleretic drugs because of its laxative properties (Tierra, 1990; Kolbl, 1961; Wichtl, 1994b). The laxative sennosides A and B, as glycosides, are inactive precursors in which the sugar moiety acts as a transport group (Dreessen *et al.*, 1981). The glycosides are hydrolysed in the organism into their aglycones at least in part by the action of bacterial enzymes. By influencing the water and electrolyte transport in the colon, these aglycones are responsible for the laxative action (Dreessen *et al.*, 1981).

(b) Anticancer activity: Emodin provides anticancer activity (Duke, 1985a). Extracts of *Rheum palmatum* caused significant tumour necrosis in a mouse study using an implanted sarcoma 37 system (Belkin and Fitzgerald, 1952; Kubo *et al.*, 1992). Aloe-emodin has been tested in mice with P-388 lymphocytic leukaemia and shown to have tumour inhibition properties. However, the activity of aloe-emodin in this study varied with the extraction method used to concentrate aloe-emodin for testing purposes (Kupchan and Karim, 1976). Aloe-emodin has been shown to have anticancer activity in the lymphocytic leukaemia and Walker carcinosarcoma tumour systems (Perdue and Hartwell, 1996). Rhein and emodin have been shown to inhibit the further growth of mammary carcinoma and Ehrlich-ascites-carcinoma in mice (List and Horhammer, 1969–1979).

Possible genotoxicity of senna-type laxative products has been reported based on studies with bacteria, but no evidence suggests a risk for mammalian or human systems (Brusick and Mengs, 1997). At high doses, emodin may act as a carcinogen (Masuda and Ueno, 1984; Morita *et al.*, 1988); however, studies have shown antimutagenic properties when administered (Ito *et al.*,

Copyright © 2000 John Wiley & Sons, Ltd. 

1986). The possible anticancer role of aloe emodin and other anthraquinones remains uncertain, but three of the most common chemotherapy agents (i.e. daunomycin, adryamicin and mitomycin C) are quinone derivatives. More research is needed to confirm the potential anticancer role of anthraquinones present in Turkish rhubarb (Driscoll *et al.*, 1974).

### Kelp (*Laminaria digitata* Lmx.)

**Composition.** Kelp contains abundant minerals and significant quantities of iodine (Blumenthal, 1998), calcium, potassium, magnesium, phosphorus, iron and silicon (Lunde, 1970; National Research Council, 1981). Total iodine varies between 0.1% to 0.8% (Bradley, 1992a; Newall *et al.*, 1996). Kelp used as a food and/or for a medicinal product should not exceed arsenic levels above 3.0 ppm and lead levels above 10.0 ppm based on the internationally recognized Food Chemicals Codex (National Research Council, 1981).

**Mechanism of action.** (a) *Antiinflammatory and demulcent action*: The alginates in kelp largely resist hydrolysis by the stomach acids and enzymes, and therefore act as a demulcent and emollient to the digestive system and increase the amount of fermentable material in the colon (Behall, 1997). The short-chain fatty acids produced are used as an energy source by colonocytes and may inhibit hepatic cholesterol synthesis and bring the associated health benefits of enhanced beneficial intestinal microflora, such as bifidobacteria. This effect is also produced by the inulin of burdock root and the mucilage of slippery elm bark. As with other soluble fibres, the alginates have a soothing and cleansing effect on the digestive tract and are known to assist in the prevention of absorption of toxic metals like mercury, cadmium, plutonium and caesium (Castleman, 1991).

(b) *Protective effect*: Kelp is best recognized for its ability to protect the body against radiation. Studies have shown that alginate supplements can reduce strontium-90 absorption from the intestinal tract by as much as 83% (Sutton *et al.*, 1971; Gong *et al.*, 1991; Castleman, 1991). The US Atomic Energy Commission guidelines advocate 2 tablespoons of alginate supplement per day to prevent strontium-90 absorption and related cancers, including leukaemia, bone cancer, and Hodgkin's disease.

(c) *Preventive and anticancer effect*: The viscous fibre of kelp has several direct and indirect anticancer effects (Salyers *et al.*, 1978). Based on both epidemiological and biological data, *Laminaria* is thought to be a factor contributing to the relatively low breast cancer rates reported in Japan (Teas, 1983). Possible mechanisms proposed by the author include: (1) kelp's nondigestible fibre increases faecal bulk and reduces bowel transit time; (2) kelp changes the post-hepatic metabolism of sterols, having an overall antilipaemic action, lowering cholesterol; (3) it contains an antibiotic substance, possibly brominated polyphenolic compounds, which positively influence faecal ecology and favours beneficial microflora; and (4) it contains laminarin (1–3 beta glucan) which alters the enzymatic activity of faecal flora.

(d) *Immunostimulatory and antitumour effect*: Several studies also document a direct, stimulatory effect of seaweed on the immune system (Taylor *et al.*, 1981; Wacker *et al.*, 1970). Kelp stimulates a host-mediated immune response, which, in animal studies, has been shown to exhibit 95% tumour inhibition, and complete tumour regressions in 6 of 9 animals tested (Yamamoto *et al.*, 1974, 1977). *In vitro* studies of the hot water extract of *Laminaria* on human KB cancer cells showed marked cytotoxic activity, noting more than 50% destruction of cancer cells (Chenieux *et al.*, 1980). Antitumour activity is also noted for the crude fucoidan fraction prepared from the roots of *Laminaria* species (Chida and Yamamoto, 1987). Kelp also has documented antiviral activity against influenza virus due to a very active inhibitor of viral and bacterial neuraminidase (Kathan, 1965).

(e) *Source of iodine*: Kelp is a good source of bioavailable iodine, an essential mineral and major component of thyroxine and triiodothyronine, hormones responsible for maintaining cellular metabolic rates. At least 1 mg of iodine per week (approximately 50 mg annually) is necessary to maintain adequate levels of these hormones (Brooks and Batchelder, 1996). Iodine also helps control cyclical breast lumps and cysts that precede breast cancer (Ghent *et al.*, 1993; Dedyna, 1997). Iodine is hypothesized to exert antioestrogen effects by reducing the sensitivity of oestrogen receptors to circulating oestrogen (Dedyna, 1997).

(f) *Hydrasorbent laxative action*: Hydrasorbent laxatives, such as the alginates from kelp, are a type of bulk-forming laxative which increase to more than 20 times their original volume by absorbing water. This large swell-volume is much greater than other types of bulk laxatives such as psyllium, cellulose and bran, which swell very little, compared with alginates.

Compared with other bulk laxatives, kelp alginates are more effective than other bulk laxatives in treating habitual constipation and gastric bloating because they increase swell-volume acting specifically in intestinal juices rather than water or gastric juices. In addition, alginates reduce intestinal transit time, soothe the intestinal mucosa, have acceptable taste and are non-irritating (Mulinos and Jerzy-Glass, 1953).

### Watercress (*Nasturtium officinale* R. Br.)

**Composition.** Watercress contains large amounts of mustard oil glycosides called glucosinolates, specifically gluconasturtiin, which is then hydrolysed to 2- phenethyl isothiocyanate (PEITC). PEITCs give watercress its characteristic aroma and produce the characteristic tingling sensation on the tongue (Harborne and Herbert, 1993). Watercress is a rich source of vitamins A and C, and trace minerals including sulphur, iodine, calcium and manganese (Wealth of India, 1991).

**Mechanism of action.** (a) *Anticarcinogenic activity*: Animal studies with PEITC demonstrate clear inhibition of 4-methylnitrosamino-1-3-pyridyl-1-butanone (NNK) induced lung tumorigenesis (Hecht, 1997). One chemoprevention study of lung cancer with rats and mice using isothiocyanates found that both PEITC and benzyl isothiocyanates (BITC) are effective inhibitors of NNK tumour induction; however, only BITC inhibits benzo-[a]pyrene (BaP) induced lung tumorigenesis. BaP is another major lung carcinogen found in tobacco smoke (Hecht, 1996, 1997, 1999). Watercress has been used for the prevention and treatment of lung and other cancers in

Copyright © 2000 John Wiley & Sons, Ltd. 

**Table 1. Biological activity of individual herbs in Flor-Essence™**

| Plant name/therapeutic action | Anti carcinogenic | Anti oxidant | Cytotoxic/Anti-tumour | Antiinflammatory | Immuno stimulant | Anti microbial | Choleretic | Other |
|---|---|---|---|---|---|---|---|---|
| **Burdock** *(Arctium lappa L.)* | ++ | ++ | ++ | + | | + | | Antidiabetic |
| **Red clover herb** *(Trifolium pratense L.)* | ++ | ++ | | | ++ | + | + | Antioestrogenic/ Antiangiogenesis |
| **Blessed thistle** *(Cnicus benedictus L.)* | | | ++ | ++ | | ++ | ++ | Tonifying |
| **Slippery elm bark** *(Ulmus rubra Muhl.)* | | ++ | + | ++ | | | | Demulcent |
| **Sheep sorrel** *(Rumex acetosella)* | | + | ++ | + | | + | | Laxative/Antidiuretic |
| **Turkish rhubarb root** *(Rheum palmatum)* | + | | ++ | | | + | ++ | Antispasmodic/ Vasorelaxant |
| **Kelp** *(Laminaria digitata Lmx.)* | + | | + | + | ++ | + | + | Laxative/Nutritional iodine supplement |
| **Watercress** *(Nasturtium officinale R. Br.)* | ++ | | | | | | ++ | Antioestrogenic/ Nutritional supplement |

\+ Some evidence
++ Strong evidence

Copyright © 2000 John Wiley & Sons, Ltd.

humans (Kelloff *et al.*, 1996; Chung *et al.*, 1992a, 1992b). In a study of 11 smokers who consumed a diet rich in watercress, the urine levels of iso-NNAL-N-oxide (NNL), a metabolite of NNK, were not affected (Hecht *et al.*, 1995). This finding suggests that PEITC inhibits the metabolic activation of NNK in *humans* (Carmella *et al.*, 1997). PEITC also has cytotoxic activity and activates detoxification enzymes in cancerous cells, thereby reducing the growth of chemically-induced tumours (Kelloff *et al.*, 1996; Caporaso *et al.*, 1994).

(b) *Antioestrogenic activity*: Indoles, also present in watercress, have been shown to have antioestrogenic activity. Cruciferous vegetables may help to prevent breast, prostate and other hormone-related cancers by enzymatically deactivating oestrogen and eliminating it from the body (Michnovicz and Bradlow, 1990). *Oestrogen dominance* is a skewed oestrogen to progesterone ratio often measured as a high blood level of oestradiol, that is associated with many hormone-related diseases including breast, ovarian, uterine, prostate and testicular cancers, (Lee, 1993, 1990a, 1990b; Lee *et al.*, 1991) and it is often caused by a dietary deficiency in omega-3 essential fatty acids (EFAs) coupled with an excess of omega-6 EFAs, which act as precursors for several hormones (Siguel, 1997, 1998; Kushi *et al.*, 1992; Erasmus, 1993). Xenoestrogens (synthetic oestrogens) in the diet and environment, such as from soft plastics, growth hormones, HRT and pesticides, are also implicated in causing oestrogen dominance (Raloff, 1993). Research has shown that xenoestrogens and the human oestrogens, oestradiol and oestrone, can form highly carcinogenic complexes with peroxidized lipids which are then transported right into the sensitive oestrogen receptor tissues of the body where they act as powerful free radical causing agents and cause DNA damage; phytoestrogens and the human oestrogen, oestriol (that predominates during pregnancy) do not form these carcinogenic complexes. Countries like Australia and Denmark, unlike the USA and Canada, use birth control pills and HRT prescriptions that are based on oestriol rather than oestradiol or oestrone (Zava, 1998 personal communication).

Research has demonstrated that an excess of omega-6 EFAs promotes high blood levels of oestradiol, a marker for high susceptibility to breast cancer (Kushi *et al.*, 1992; Holm, 1993; Howe *et al.*, 1990).

Watercress, cabbage, broccoli, cauliflower, Brussels sprouts, kale, mustard greens and collard greens, bok choy and turnips contain specific indoles that activate enzymes in the body that deactivate and dispose of excess oestrogen thereby reducing breast cancer risk (Bresnick *et al.*, 1990). Indole-3-carbinol accelerates oestrogen deactivation by about 50% at 500 mg per day, an equivalent of 14 ounces of raw cabbage. Heavy cooking destroys indoles and is not recommended for an anticancer diet (Carper, 1993). Unfortunately, many people in our culture are deficient in omega-3 fatty acids and have excesses of omega-6 EFAs (20x higher in the diet than omega-3 EFAs) and this can lead to many serious health problems including increased risk of cancer (Yam, 1996; Allman *et al.*, 1995).

(c) *Nutritional supplement and digestive aid*: In Europe, watercress is popular as a blood cleanser and part of several phytopharmaceutical choleretic preparations (a choleretic increases the flow of bile into the intestines) (Wichtl, 1994a). The fresh leaves are a superior food medicine containing high levels of vitamins A and C, and iodine. Analysis of watercress from India showed the following levels: vitamin A 4720 I.U.; thiamine 0.08; riboflavin 0.16; niacin 0.8, and ascorbic acid 77 mg per 100 g (Wealth of India, 1991). However, vitamin and mineral content varies considerably with the source (Duke, 1992a). Its calcium is well assimilated by the human body, and the herb has been traditionally used as a remedy for vitamin deficiency (Wealth of India, 1991).

## CONCLUSION

The evidence supporting the activities of each of the herbs on the Flor-Essence™ mixture is summarized in Table 1. Some of the herbs have demonstrated anticancer, cytotoxic and immunomodulatory activity and the individual components (i.e. phytoestrogens, anthraquinones, and flavonoids) may be a source of therapeutic value for the prevention and treatment of cancer.

Herbalists believe that the synergistic interaction of herb constituents is critical to their beneficial treatment effect and limited side effects of herbs compared with synthetically produced drugs. Proponents of herbal therapies and particularly Flor-Essence™ also claim that its effect is dependent on the herbs being present in the correct proportions in accordance with the approved formulation. Basic and clinical research on Flor-Essence™ is limited. In addition, there are no data on the possible synergistic effect of individual herbs in the final product, and research on individual herbs may not be applicable to the whole preparation. No attempt has been made to translate dose and routes of administration of individual herbs to that of the oral administration, twice per day of 60 mL of Flor-Essence™ tea. Because each herb in the preparation has specific biological activity and they may produce a combined beneficial effect, further investigation is required.

Only carefully designed clinical studies will confirm the anecdotal reports from cancer patients. The interesting historical origin of the formula and the subsequent effective use as an anticancer agent make this alternative agent an excellent candidate for further evaluation. A controlled clinical study to determine the effect of the Flor-Essence™ on quality of life for cancer patients is being planned by the UT-CAM, in collaboration with the Tzu Chi Institute for Complementary and Alternative Medicine and the British Columbia Cancer Agency. The study is a randomized, parallel, Phase II trial that is anticipated to begin in late 1999.

### Acknowledgements

This work was supported by the National Institutes of Health grant number 5 U24 CA66826-03 through the National Center for Complementary/Alternative Medicine and the National Cancer Institute. The authors acknowledge Tina Ramirez, Research Assistant at UT-CAM, for assistance with the preparation of this manuscript.

Copyright © 2000 John Wiley & Sons, Ltd. 

## REFERENCES


Agarwal, R., and Mukhtar, H. (1996). Cancer chemoprevention by polyphenols in green tea and artichoke. *Adv. Exp. Med. Biol.* **401**, 35–50.

Allman, M., Pena, M., and Pang, D. (1995). Supplementation with flaxseed oil versus sunflowerseed oil in healthy young men consuming a low fat diet: effects on platelet composition and function. *Eur. J. Clin. Nutr.* **49**, 169–178.

American Cancer Society (1993). Questionable methods of cancer management: The Committee for Freedom of Choice in Medicine, Inc. *CA Cancer J. Clin.* **43**, 117–123.

Anderson, J. J. B., and Garner, S. C. (1997). The effects of phytoestrogens on bone. (Review). *Nutr. Res.* **17**, 1617–1632.

Aykroyd, W. R., and Doughty, J. (1982). Legumes in human nutrition. Food and Agriculture Organization of the United Nations. *FAO Food Nutr. Pap.* **20**, 1–152.

Barnes, S. (1995). Effect of genistein on *in vitro* and *in vivo* models of cancer. *J. Nutr.* **125** (3, Suppl.), 777S–783S.

Barnes, S., Grubbs, C., Setchell, K. D., and Carlson, J. (1990). Soybeans inhibit mammary tumors in models of breast cancer. *Prog. Clin. Biol. Res.* **347**, 239–253.

Barnes, S., and Peterson, G. (1995). Biochemical targets of the isoflavone genistein in tumor cell lines. *Proc. Soc. Exp. Biol. Med.* **208**, 101–108.

Barnes, S., Peterson, G., Grubbs, C., and Setchell, K. (1994). Potential role of dietary isoflavones in the prevention of cancer. *Adv. Exp. Med. Biol.* **354**, 135–147.

Behall, K. M. (1997). Dietary fiber: nutritional lessons for macronutrient substitutes. *Ann. N Y Acad. Sci.* **819**, 142–154.

Belkin, M., and Fitzgerald, D. (1952). Tumor damaging capacity of plant materials. 1. Plants used as cathartics. *J. Natl Cancer Inst.* **13**, 139–155.

Beveridge, R. J., Stoddart, J. F., Szarek, W. A., and Jones, J. K. N. (1969). Some structural features of the mucilage from the bark of *Ulmus fulva* (Slippery elm mucilage). *Carbohydr. Res.* **9**, 429–439.

Beveridge, R. J., Szarek, W. A., and Jones, J. K. N. (1971). Isolation of three oligosaccharides from the mucilage from the bark of *Ulmus fulva* (Slippery Elm musilage). Synthesis of O-(3-O-methyl-B-D-galactopyranosyl)-(1-4)-L-rhamnose. *Carbohydr. Res.* **19**, 107–116.

Biggs, D. R., and Lane, G. A. (1978). Identification of isoflavones calycosin and pseudobatigenin in *Trifolium pratense*. *Phytochemistry* **17**, 1683–1684.

Blumberger, W., and Glatzel, H. (1996). Uber die speichelwirksamkeit von Bitterstoffen. In *Pflanzliche Bitterstoffe. Planta Med. Supplement*, ed. by E. Schratz, pp. 52–60. Hippokrates, Stuttgart.

Blumenthal, M. (ed). (1998). *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*, 1st edn, pp. 92, 340–341. American Botanical Council, Boston, MA.

Bradley, P. R. (ed). (1992a). Holy thistle. In British Herbal Compendium. Volume 1. *A Handbook of Scientific Information on Widely Used Plant Drugs*, pp. 126–127. British Herbal Medicine Association Bournemouth, Dorset.

Bradley, P. R. (ed). (1992b). Slippery Elm Bark in British Herbal Compendium Vol. 1, p. 204. British Herbal Medicine Association Bournemouth, Dorset.

Bresnick, E., Birt, D. F., Woterman, K., Wheeler, M., and Markin, R. S. (1990). Reduction in mammary tumorigenesis in the rat by cabbage and cabbage residue. *Carcinogenesis* **11**, 1159–1163.

Brooks, S., and Batchelder, H. J. (1996). Phytochemical list and active ingredients. *The Protocol J. Bot. Med.* **1**, 249–282.

Brusick, D., and Mengs, U. (1997). Assessment of the genotoxic risk from laxative senna products. *Environ. Mol. Mutagen.* **29**, 1–9.

Canadian Breast Cancer Research Initiative. *Essiac: An Information Package*, Dec 1996. http://www.breast.cancer.ca

Caporaso, N., Whitehouse, J., Monkman, S. et al. (1994). *In vitro* but not *in vivo* inhibition of CYP2D6 by phenethyl isothiocyanate (PEITC), a constituent of watercress. *Pharmacogenetics* **4**, 275–280.

Carmella, S. G., Borukhova, A., Akerkar, S. A., and Hecht, S. S. (1997). Analysis of human urine for pyridine-N-oxide metabolites of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanoni, a tobacco-specific lung carcinogen. *Cancer Epidemiol Biomarkers Prev.* **6**, 113–120.

Carper, J. (1993). *Food Your Miracle Medicine*, p. 459. Harper Collins Publishing, Inc., New York.

Cassady, J. M., Zennie, T. M., Chae, Y. H., Ferin, M. A., Portunodo, N. E., and Baird, W. M. (1988). Use of a mammalian cell culture benzo(a)pyrene metabolism assay for the detection of potential anticarcinogens from natural products: inhibition of metabolism by biochanin A, an isoflavone from *Trifolium pratense L. Cancer Res.* **48**, 6257–6261.

Castleman, M. (1991). Kelp. In *The Healing Herbs. The Ultimate Guide to the Curative Power of Nature's Medicines*, pp. 229–232. Rodale Press/Book Reader Service Emmaus, PA.

Chenieux, J. C., Verbist, J. F., Biard, J. F. et al. (1980). Contenant des substances antimitotiques. *Planta Med.* **Suppl** 152–162.

Chida, K., and Yamamoto, I. (1987). Antitumor activity of a crude fucoidan fraction prepared from the roots of kelp (*Laminaria* species). *Kitasato Arch. Exp. Med.* **60**, 33–39.

Chung, F. L., Morse, M. A., and Eklind, K. I. (1992a). New potential chemopreventive agents for lung carcinogenesis of tobacco-specific nitrosamine. *Cancer Res.* **52** (9, Suppl.), 2719S–2722S.

Chung, F. L., Morse, M. A., Eklind, K. I., and Lewis, J. (1992b). Quantitation of human uptake of the anticarcinogen phenethyl isothiocyanate after a watercress meal. *Cancer Epidemiol. Biomarkers Prev.* **1**, 383–388.

Clarke, R., Hilakivi-Clarke, L., Cho, E., James, M. R., and Leonessa, F. (1996). Estrogens, phytoestrogens and breast cancer. (Review). *Adv. Exp. Med. Biol.* **401**, 63–85.

Constantinou, A., and Huberman, E. (1995). Genistein as an inducer of tumor cell differentiation: possible mechanisms of action. *Proc. Soc. Exp. Biol. Med.* **208**, 109–115.

Dedyna, K. (1997 September). Iodine: bosom buddy. *Victoria Times Colonist*.

Derwick, P. (1997). Biosynthesis of pterocarpan phytoalexins in *Trifolium pratense*. *Phytochemistry* **16**, 93–97.

Dombradi, C., and Foldeak, S. (1966). Screening report on the antitumor activity of purified *Arctium lappa* extracts. *Tumori* **52**, 173–176.

Draper, C. R., Edel, M. J., Dick, I. M., Randall, A. G., Martin, G. B., and Prince, R. L. (1997). Phytoestrogens reduce bone loss and bone resorption in oophorectomized rats. *J. Nutr*, **127**, 1795–1799.

Dreessen, M., Eyssen, H., and Lemli, J. (1981). The metabolism of sennosides A and B by the intestinal microflora: *in vitro* and *in vivo* studies on rat and mouse. *J. Pharm. Pharmacol.* **33**, 678–681.

Driscoll, J. S., Hazard, Jr H. B., Wood Jr, and Goldin, A. (1974). Structure–antitumor activity relationships among quinone derivatives. *Cancer Chem. Rep. Part 2* **4**, 1–27.

Duh, P. D. (1998). Antioxidant activity of burdock (*Arctium lappa* Linne): its scavenging effect on free-radical and active oxygen. *J. Am. Oil Chem. Soc.* **75**, 455–461.

Duke, J. A. (1985a). Emodin. In *Handbook of Medicinal Herbs*, p. 572. CRC Press, Boca Raton, FL.

Duke, J. A. (1985b). *Rumex crispus* L. In *Handbook of Medicinal Herbs*, pp. 414–415. CRC Press, Boca Raton, FL.

Duke, J. A. (1985c). Turkish rhubarb. In *Handbook of Medicinal Herbs*, p. 404. CRC Press, Roca Raton, FL.

Duke, J. A. (1985d). *Ulmus rubra* Muhl. (Ulmaceae). In *Handbook of Medicinal Herbs*, pp. 495–496. CRC Press, Boca Raton, FL.

Duke, J. A. (1989). The synthetic bullet vs. the herbal shotgun shell. *Herbal Gram* **18–19**, 12–13.

Duke, J. A. (1990). *An Herb a Day* (column): Red clover. *The Business of Herbs* Vol. **8**, 8–9.

Duke, J. A. (1992a). *Handbook of Biologically Active Phyto-*


Copyright © 2000 John Wiley & Sons, Ltd. 

*chemicals and their Activities*, p.32. CRC Press, Boca Raton, FL.
Duke, J. A. (1992b). *Handbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants*, pp. 186–187. CRC Press, Boca Raton, FL.
Erasmus, U. (1993). *Fats That Heal, Fats That Kill.* Alive Books, Burnaby, BC, Canada.
European Scientific Cooperative on Phytotherapy (1997). Wormwood, Dandelion, Gentian. ESCOP Secretariat Argyle House, Exeter, UK.
Facino, R. M., Carini, M., Aldini, G., Bombardelli, E., Morazzoni, P., and Morelli, R. (1994). Free radical scavenging action and anti-enzyme activities of procyanidines from *Vitis vinifera. Arzneimittelforsch. Drug Res.* **44**(I), 592–601.
Fairbairn, J. W., and Muhtadi, F. J. (1972). Chemotaxonomy of anthraquinones in rumes. *Phytochemistry* **11**, 263–268.
Fernandes, C. F., and Shahani, K. M. (1990). Anticarcinogenic and immunological properties of dietary lactobacili. *J. Food Prot.* **53**, 704–710.
Flora Manufacturing and Distributing Files (1997). Academy of Agricultural Sciences of the Russian Federation Research & Manufacturing Association. Research & Development Institute of Medical & Aromatic Plants. Unpublished Report.
Flynn, R., and Roest, M. (1995). *Your Guide to Standardized Herbal Products*, pp. 3, 16–17. One World Press, 601 Granada Drive, Prescott, AZ, 86301; Library of Congress: 94–80040.
Foldeak, S., and Dombradi, G. A. (1964). Tumor-growth inhibiting substances of plant origin. I. Isolation of the active principle of *Arctium lappa. Acta Phys. Chem.* **10**, 91–93.
Foster, S., and Duke, J. A. (1990). *Sheep Sorrel in Medicinal Plants*, p. 214. Houghton Mifflin Co., New York.
Fotsis, T., Pepper, M., Adlercreutz, H., Hase, T., Montesano, R., and Schweigerer, L. (1995). Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and *in vitro* angiogenesis. *J. Nutr.* **125** (3 Suppl), 790S–797S.
Franke, A. A., Custer, L. J., Cerna, C. M., and Narula, K. K. (1994). Quantitation of phytoestrogens in legumes by HPLC. *J. Agric. Food Chem.* **42**, 1905–1913.
Fraser, S. S., and Allen, C. (1977). Could Essiac Halt Cancer? *Homemaker's Magazine* **June/July/August**, 1–18.
Ghent, W. R., Eskin, B. A., Low, D. A., and Lucius, P. H. (1993). Iodine replacement in fibrocystic disease of the breast. *Can. J. Surg.* **36**, 453–460.
Gibson, G. R., Beatty, E. R., Wang, X, and Cummings, J. H. (1995). Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology* **108**, 975–982.
Gong, Y. F., Huang, Z. J., Qiang, M. Y. et al. (1991). Suppression of radioactive strontium absorption by sodium alginate in animals and human subjects. *Biomed. Environ. Sci.* **4**, 273–282.
Goodman, M. T., Wilkens, L. R., Hankin, J. H., Lyu, L. C., Wu, A. H., and Kolonel, L. N. (1997). Association of soy and fiber consumption with the risk of endometrial cancer. *Am. J. Epidemiol.* **146**, 294–306.
Gray, R. E., Fitch, M., Greenberg, M. et al. (1997). Perspectives of cancer survivors interested in unconventional therapies *J. Psychosoc. Oncol.* **15**, 149–171.
Greenwald, P. (1989). Principles of cancer prevention: diet and nutrition. In *Cancer: Principles and Practice of Oncology*, 3rd edn, pp. 167–180. ed. by V. T. DeVita Jr, S. Hellman, and S. A. Rosenberg. J. B. Lippincott, Philadelphia, PA.
Harborne, J. B., and Herbert, B. (1993). *Phytochemical Dictionary. A Handbook of Bioactive Compounds from Plants*. Taylor & Francis, Inc., London.
Hardman, J. G., and Limbird, L. E. (eds). (1996). *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th edn, pp. 888–889. McGraw-Hill, Health Professions Division, New York.
Hecht, S. S. (1996). Chemoprevention of lung cancer by isothiocyanates. *Adv. Exp. Med. Biol.* **401**, 1–11.
Hecht, S. S. (1997). Approaches to chemoprevention of lung cancer based on carcinogens in tobacco smoke. *Environ. Health Perspect.* **105** (4, Suppl.) 955–963.
Hecht, S. S. (1999). Chemoprevention of cancer by isothiocyanates, modifiers of carcinogen metabolism. *J. Nutr.* **129**, 768S–774S.
Hecht, S. S., Chung, F. L., Richie, J. P. Jr, et al. (1995). Effects of watercress consumption on metabolism of a tobacco-specific lung carcinogen in smokers. *Cancer Epidemiol. Biomarkers Prev.* **4**, 877–884.
Herman, C., Adlercreutz, T., Goldin B. R. et al. (1995). Soybean phytoestrogen intake and cancer risk. *J. Nutr.* **125**, 757S–770S.
Hidaka, H., Eida, T., Takizawa, T., Tokunaga, T., and Tashiro, Y. (1986). Effects of Fructooligosaccharides on intestinal flora and human health. *Bifidobacteria Microflora* **5**, 37–50.
Hirano, T., Gotoh, M., and Oko, K. (1994). Natural flavonoids and lignans are potent cytostatic agents against humal leukemic HL-60 cells. *Life Sci.* **55**, 1061–1069.
Holm, L. E. (1993). Treatment failure and dietary habits in women with breast cancer. *J. Natl. Cancer Inst.* **85**, 32–36.
Horn-Ross, P. L., Morrow, M., and Ljung, B. M. (1997). Diet and the risk of salivary gland cancer. *Am. J. Epidemiol.* **146**, 171–176.
Hoverstad, T. and Bjorneklett, A. (1984). Short-chain fatty acids and bowel functions in man. *Scand. J. Gastroenterol.* **19**, 1059–1065.
Howe, G. R., Hirohata, T., Hislop, T. G. et al. (1990). Dietary factors and risk of breast cancer. Combined analysis of 12 case–control studies. *J. Natl Cancer Inst.* **82**, 561–569.
Hutchens, A. R. (1973). *Slippery Elm in Indian Herbology of North America*, pp. 252–253. Shambhala Publishers, Inc., Boston, MA.
Ingram, D., Sanders, K., Kolybaba, M., and Lopez, D. (1997). Case–control study of phyto-oestrogens and breast cancer. *Lancet* **350**(9083), 990–994.
Ito, Y., Maeda, S., and Sugiyama, T. (1986). Suppression of 7,12-dimethylbenz[a]anthracene-induced chromosome aberrations in rat bone marrow cells by vegetable juices. *Mutat. Res.* **172**, 55–60.
Iwakami, S., Wu, J-B., Fazuka, Y., and Sankawa, W. (1992). Platelet activating factor (PAF) Antagonists contained in medicinal plants: Lignans and sesquiterpenes. *Chem. Pharm. Biol.* **40**, 1196–1198.
Iwu, M. M. (1993). *Handbook of African Medicinal Plants*, pp. 167–168, 188–189. CRC Press, Inc., Boca Raton, FL.
Jensen, C. D., Haskell, W., and Whittam, J. H. (1997). Long-term effects of water-soluble dietary fiber in the management of hypercholesterolemia in healthy men and women. *Am. J. Cardiol.* **79**, 34–37.
Kao, P. C., and P'eng, F. K. (1995). How to reduce risk factors of osteoporosis in Asia. (Review). *Chin. Med. J. (Engl)* **55**, 209–213.
Kathan, R. H. (1965). Kelp extracts as antiviral substances. *Ann. N Y Acad. Sci.* **130**, 390–397.
Kato, A., Ando, K., Tamura, G., and Arima, K. (1971). Effects of some fatty acid esters on the viability and transplantability of Ehrlich ascites tumor cells. *Cancer Res.* **31**, 501–504.
Kelloff, G. J., Boone, C. W., Crowell, J. A. et al. (1996). New agents for cancer chemoprevention. *J. Cell. Biochem.* **26** (Supp.), 1–28.
Kelly, G., Husband, A., and Waring, M. Promensil™. Natural plant estrogens for women experiencing midlife changes. In *Technical and Safety Bulletin*, pp. 1–11. Novogen, Inc., Stamford, CT.
Kennedy, A. R. (1995). The evidence for soybean products as cancer preventive agents. *J. Nutr.* **125** (3 Suppl), 733S–743S.
Kies, C. (1985). Non-soluble dietary fiber effects on lipid absorption and blood serum lipid patterns. *Lipids* **20**, 802–807.
Kimura, T., Furuta, H., Matsumoto, Y., and Yoshida, A. (1980). Ameliorating effect of dietary fiber on toxicities chemicals added to a diet in the rat. *J. Nutr.* **110**, 513–521.
Knight, D. C., and Eden, J. A. (1995). Phytoestrogens—a short review. *Maturitas* **22**, 167–175.
Kolbl, K. (1961). *Kolbl's Krauterfibel*, 20th edn, pp. 151–152. Kolbl Verlag, Munich, Germany.
Kraft, K. (1997). Artichoke leaf extract. Recent findings reflecting effects on lipid metabolism, liver and gastrointestinal tracts. *Phytomedicine* **4**, 369–378.
Kubo, I., Murai, Y., Soedro, I., Soetarno, S., and Sastrodihar-

Copyright © 2000 John Wiley & Sons, Ltd. 

ojo, S. (1992). Cytotoxic anthraquinones from *Rheum pulmatum*. *Phytochemistry* **31**, 1063–1065.
Kupchan, S. M., and Karim, A. (1976). Tumor inhibitors. 114. Aloe emodin: antileukemic principle isolated from *Rhamnus frangula* L. *Lloydia* **39**, 223–224.
Kurzer, M. S., and Xu, X. (1997). Dietary phytoestrogens. *Annu. Rev. Nutr.* **17**, 353–381.
Kushi, L. H., Seller, T. A., Potter, J. D. et al. (1992). Dietary fat and postmenopausal breast cancer. *J. Natl Cancer Inst.* **84**, 1092–1099.
Lamartiniere, C. A., Murrill, W. B., Manzolillo, P. A. et al. B. (1998). Genistein alters the ontogeny of mammary gland development and protects against chemically-induced mammary cancer in rats. *Proc. Soc. Exp. Biol. Med.* **217**, 358–364.
Lee, H. P., Gourley, L. D. S. W., Esteve, J., Lee., J., and Day, N. E. (1991). Dietary effect on breast cancer risk in Singapore. *Lancet* **337**, 1197–1200.
Lee, J. R. (1990a). Osteoporosis reversal: the role of progestrone. *Int. Clin. Nutr. Rev.* **10**, 384–391.
Lee, J. R. (1990b). Osteoporosis reversal with transdermal progesterone. (Letter). *Lancet* **336**, 1327.
Lee, J. R. (1991). Is natural progesterone the missing link in osteoporosis prevention and treatment. *Med. Hypotheses* **35**, 316–318.
Lee, J. R. (1993). *Natural Progesterone: the Multiple Roles of a Remarkable Hormone.* BLL Publishing, Sebastopo., CA.
Ley, R. D., and Reeve, V. E. (1997). Chemoprevention of ultraviolet radiation-induced skin cancer. *Environ. Health Perspect.* **105** (4 Suppl), 981–984.
Lin, C. C., Lu, J. M., Yang, J. J., Chuang, S. C., and Ujiie, T. (1996). Anti-inflammatory and radical scavenge effects of *Arctium lappa*. *Am. J. Chin Med.* **24**, 127–137.
List, P., and Horhammer, L. (1969–1979). Hager's Handbuch der Pharmazeutischen Praxis Vol. 2–6. Springer-Verlag, Berlin.
Lunde, G. (1970). Analysis of trace elements in seaweed. *J. Sci. Food Agric.* **21**, 416–418.
Luo, J., Rizkalla, S., Alamowitch, C. et al. (1996). Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. *Am. J. Clin. Nutr.* **63**, 939–945.
Malterud, K. E., Farbrot, T. L., Huse, A. E., and Sund, R. B. (1993). Antioxidant and radical scavenging effects of anthraquinones and anthrones. *Pharmacology* **47** (Suppl 1), 77–85.
Maruta, Y., Kawabata, J., and Niki, R. (1995). Antioxidative caffeoylquinic acid derivatives in the roots of burdock *(Arctium lappa* L.). *J. Agric. Food Chem.* **43**, 2592–2595.
Masuda, T., and Ueno, Y. (1984). Microsomal transformation of emodin into a direct mutagen. *Mutat. Res.* **125**, 135–144.
Messina, M., Persky, V., Setchell, K. D. R., and Barnes, S. (1994). Soy intake and cancer risk: a review of *in vitro* and *in vivo* data. *Nutr. Cancer* **21**, 113–131.
Michnovicz, J. J., and Bradlow, H. L. (1990). Induction of estradiol metabolism by dietary indole-3-carbinol in humans. *J. Natl Cancer Inst.* **82**, 947–949.
Miksicek, R. J. (1993). Commonly occurring plant flavonoids have estrogenic activity. *Mol. Pharmacol.* **44**, 37–43.
Miyamoto, K., Nomura, M., Sasakura, M., Matsui, E., Koshiura, R., and Murayama, T. (1993). Antitumor activity of cenothein B, a unique macrocyclic ellagatanin. *Jpn J. Cancer Res.* **84**, 99–103.
Morita, H., Umeda, M., Masuda, T., and Ueno, Y. (1988). Cytotoxic and mutagenic effects of emodin on cultured mouse carcinoma FM3A cells. *Mutat. Res.* **204**, 329–332.
Morita, K., Kada, T., and Namiki, M. (1984). A desmutagenic factor isolated from burdock (*Arctium lappa* Linne). *Mutat. Res.* **129**, 25–31.
Morita, K., Nishijima, Y., and Kada, T. (1985). Chemical nature of a desmutagenic factor from burdock (*Arctium lappa* Linne). *Agric. Biol. Chem.* **49**: 925–932.
Moritani, S., Nomura, M., Takeda, Y., and Miyamoto, K. (1996). Cytotoxic components of bardanae fructos (Goboshi). *Biol. Pharm. Bull.* **19**, 1515–1517.
Morton, M. S., Bundred, N., McMichealphillips, D. F., Harding, C., Nicholson, R. I., and Griffiths, K. (1997a). Phytoestrogens and breast cancer. *Endocr. Relat. Cancer* **4**, 331–339.
Morton, M. S., Chan, P. S., Cheng, C. et al. (1997b). Lignans and isoflavonoids in plasma and prostatic fluid in men: samples from Portugal, Hong Kong, and the United Kingdom. *Prostate* **32**, 122–128.
Mousavi, Y., and Adlercreutz, H. (1993). Genistein is an effective stimulator of sex hormone-binding globulin production in hepatocarcinoma human liver cancer cells and suppresses proliferation of these cells in culture. *Steroids* **58**, 301–304.
Mulinos, M. G., and Jerzy-Glass, G. B. (1953). The treatment of constipation with a new hydrasorbent material derived from kelp. *Gastroenterology* **24**, 383–393.
Murkies, A. (1998). Phytoestrogens—what is the current knowledge? (Review). *Aust. Fam. Physician* **27** (Suppl 1), S47–S51.
National Research Council (1981). *Food Chemicals Codex. Food and Nutrition Board, Division of Biological Sciences, Assembly of Life Sciences*, pp. 157–158. National Academy Press, Washington, DC.
Newall, C. A., Anderson, L. A., and Phillipson, J. D. (1996). *Herbal Medicines. A Guide for Health Care Professionals*, pp. 250–252. The Pharmaceutical Press, London.
Nwannenna, A. I., Lundh, T. J., Madej, A., Gredriksson, G., and Bjornhag, G. (1995). Clinical changes in ovariectomized ewes exposed to phytoestrogens and 17 beta-estradiol implants. *Proc. Soc. Exp. Biol. Med.* **208**, 92–97.
Odin, A. P. (1997). Vitamins as antimutagens: Advantages and some possible mechanisms of antimutagenic action. *Mutat. Res.* **386**, 39–67.
Pedersen, M. (1987). *Nutritional Herbology*, pp. 236–238. Bradley Pederson Publishing, Bountiful, Utah.
Perdue, R., and Hartwell, J. (1996). Plants and cancer. *Proceedings from the 16th Annual Meeting of the Society of Economic Botanical Cancer Treatment Representatives* **60**, 973.
Peterson, G., and Barnes, S. (1993). Genistein inhibition of the growth of human breast cancer cells: independence from estrogen receptors and the multi-drug resistence gene. *Biochem. Biophys. Res. Commun.* **157**, 183–189.
Pizzorno, J. E. (1993). Procyanidolic oligomers. In A Textbook of Natural Medicine Vol. 1, pp. 795–797. Bastyr College Publications, Seattle, WA.
Potter, J. D., and Steinmetz,K. (1996). Vegetables, fruit and phytoestrogens as preventive agents. *IARC Sci. Publ.* **139**, 61–90.
Raloff, J. (1993). Ecocancers: do environmental factors underlie a breast cancer epidemic? *Sci. News* **144**, 10–13.
Reinli, K., and Block, G. (1996). Phytoestrogen content of foods—a compendium of literature values. *Nutr. Cancer* **26**, 126–148.
Reynolds, J. E. F., and Martindale, W. (1993). *The Extra Pharmacopoeia. The Universally Acclaimed Source of Drug Information*, 30th edn, pp. 1355–1356. The Pharmaceutical Press, London.
Rickard, S. E., Jenab, M., Tou, J. C. L., Nesbitt, P. D., and Thompson, L. U. (1998). *Anticancer effects and availability of flaxseed lignans. Proceedings of the 57th Flax Institute of the U.S.* pp. 8–14. The Flax Institute, N. Dakota State University, Fargo, ND.
Risch, H. A., Weiss, N. S., Clarke, E. A., and Miller, A. B. (1988). Risk factors for spontaneous abortion and its recurrence. *Am. J. Epidemiol.* **128**, 420–430.
Roberfroid, M. (1993). Dietary fiber, inulin, and oligofructose: a review comparing their physiological effects. *Crit. Rev. Food Sci. Nutr.* **33**, 103–148.
Rodriguez, E., Towers, G. H. N., and Mitchell, J. C. (1976). Biological activities of sesquiterpene lactones. *Phytochemistry* **15**, 1573–1580.
Root, H. F., and Banker, M. L. (1925). Inulin and artichokes in the treatment of diabetes. *Arch. Intern. Med.* **36**, 126–145.
Rose, D. P. (1992). Dietary fiber, phytoestrogens, and breast cancer. (Review). *Nutrition* **8**, 47–51.
Sachse, J. (1974). Die bestimmung ostrogener isoflavone und cumostrol in klee (*Trifolium pratense* L. und *Trifolium repens L.). J. Chromatogr.* **96**, 123–136.
Saloniemi, H., Wahala, K., Nykanen-Kurki, P., Kallela, K., and Saastamoinen, I. (1995). Phytoestrogen content and

Copyright © 2000 John Wiley & Sons, Ltd. 

estrogenic effect of legume fodder. *Proc. Soc. Exp. Biol. Med.* **208**, 13–17.
Salyers, A. A., Palmer, J. K., and Wilkins, T. D. (1978). Degradation of polysaccharides by intestinal bacterial enzymes. *Am. J. Clin. Nutr.* **31**, S128–S130.
Saunders, W. B. (1994). *Dorlands Illustrated Medical Dictionary.* W. B Saunders, Philadelphia, PA.
Schneider, G., and Lachner, I. (1987). A contribution to analytics and pharmacology of cnicin. *Planta Med.* **53**, 247–251.
Schroder, H., Merz, H., Steffen, R., and Muller, W. (1990). Differential *in vitro* anti-HIV activity of natural lignans. *Z. Naturofosch.* **45c**, 1215–1221.
Setchell, K. D. R., and Adlercreutz, H. (1988). Mammalian lignans and phytoestrogens. Recent studies on their formation, metabolism and biological role in health and disease. In *Role of the Gut Flora in Toxicity and Cancer*, ed. by I. R. Rowland, pp. 315–345 Academic, London.
Shahani, K. M., Fernandes, C. F., and Amer, V. (1989). Immunologic and therapeutic modulation of gastrointestinal microecology by Lactobacilli. *Microecology & Therapy* **18**, 103–104.
Shar, D. (1993). Red clover. In *Thirty Plants That Can Save Your Life*, pp. 98–102. Elliott & Clark Publishing, Washington, DC.
Siguel, E. N. (1997). Dietary modulation of omega-3-omega-6 polyunsaturated fatty acid ratios in patients with breast cancer. *J. Natl. Cancer Inst.* **89**, 1123–1131.
Siguel, E. N. (1998). Dietary modulation of omega-3-omega-6 polyunsaturated fatty acid ratios in patients with breast cancer. (Letter, Comment). *J. Natl. Cancer Inst.* **90**, 629–631.
Silver, A. A., and Krantz, J. C. (1931). The effect of the ingestion of burdock root on normal and diabetic individuals: a preliminary report. The ingestion of burdock root. *Ann. Intern. Med.* **5**, 274–284.
Slavin, J., Jacobs, D., and Marguart, L. (1997). Whole-grain consumption and chronic disease: protective mechanisms. (Review). *Nutr. Cancer* **27**, 14–21.
Stephens, F. O. (1997a). Breast cancer: aetiological factors and associations (a possible protective role of phytoestrogens). *Aust. N Z J. Surg.* **67**, 755–760.
Stephens, F. O. (1997b). Phytoestrogens and prostate cancer: possible preventive role. *Med. J. Aust.* **167**, 138–140.
Sticher, O. (1997). Plant mono, di- and sesquiterpenoids with pharmacological or therapeutic activity. In *New Natural Products and Plant Drugs with Pharmacological, Biological and Therapeutic Activity*, ed. by H. Wagner and P. Wolff, pp. 137–175 Springer-Verlag, Berlin.
Stitch, S. R., Toumba, J. K., Groen, M. B. et al. (1980). Occurrence of lignans, enterolactone and enterodiol in man and animal species. *Nature* **287**, 238.
Stitt, P. A. (1990). *Why George Should Eat Broccoli*, p. 399. Dougherty Co., Milwaukee, WI.
Sutton, A., Harrison, G. E., Carr, T. E. F., and Barltrop, D. (1971). Reduction in the absorption of dietary strontium in children by an alginate derivative. *Int. J. Radiat. Biol.* **19**, 79–85.
Takasugi, M., Kawashima, S., Katsui, N., and Shirata, A. (1987). Two polyacetylenic phytoalexins from *Arctium lappa. Phytochemistry* **26**, 2957–2958.
Taylor, W. A., Sheldon, D., and Spicer, S. W. (1981). Adjuvant and suppressive effects of grass conjuvae and other alginate conjugates on IgG and IgE antibody responses in mice. *Immunology* **44**, 41–50.
Teas, J. (1983). Dietary intake of laminaria, a brown seaweed, and breast cancer prevention. *Nutr. Cancer* **4**, 217–222.
The University of Texas—Houston Center for Alternative Medicine. 1998 http://www.sph.uth.tmc.edu/utcam/default.htm
Thomas, R. (1993). *The Essiac Report: The True Story of a Canadian Herbal Cancer Remedy and of the Thousands of Lives it Continues to Save*, 3rd edn. Alternative Treatment Information Network, Los Angeles, CA.
Tierra, M. (1990). *The Way of Herbs*, pp. 221–222. Simon Schuster, Inc., USA.
Traganos, F., Ardelt, B., Halko, N., Bruno, S., and Darzynkiewics, Z. (1992). Effects of genistein on the cell growth and cell cycle progression of normal human lymphocytes and human leukemic MOLT-4 and HL-60 cells. *Cancer Res.* **52**, 6200–6208.
Turner, N., and Kuhnlein, H. (1991). Traditional plant foods of Canadian indigenous peoples. Nutrition, botany and use. In Food and Nutrition in History and Anthropology Vol. 8, p. 222. Gordon & Breach Science Publishers, Philadelphia.
Umehara, K., Endoh, M., Miyase, T., Kuroyanagi, M., and Ueno, A. (1992). Studies on differentiation-inducing activities of triterpenes. *Chem. Pharm. Bull.* **40**, 401–405.
Umehara, K., Nakamura, M., Miyase, T., Kuroyangi, M., and Ueno, A. (1996). Studies on differentiation inducers. VI. Lignan derivatives from *Arctium fructus*. *Chem. Pharm. Bull.* **44**, 2300–2304.
Vanhaelen-Fastre, R. (1973). Constitution and antibiotic properties of the essential oil of *Cnicus benedictus*. *Planta Med.* **24**, 165–175.
Vanhaelen-Fastre, R. (1974). Constituants polyacetyleniques de *cnicus benedictus*. *Planta Med.* **25**, 47–59.
Vanhaelen-Fastre, R., and Vanhaelen, M. (1976). Antibiotic and cytotoxic activity of *cnicin* and of its hydrolysis products. Chemical structure–biological activity relationship. *Planta Med.* **29**, 179–189.
Vanhaelen, M., and Vanhaelen-Fastre, R. (1975). Lactonic lignans from *Cnicus benedictus*. *Phytochemistry* **14**, 2709.
Wacker, A., Chandra, P., Haenszel, I., and Gericke, D. (1970). Effect of polyanions on the antibody formation by spleen cells. *Hoppe Seylers Z. Physiol. Chem.* **351**, 1273–1276.
Wahlquist, M. L., and Dalais, F. S. (1997). Phytoestrogens: emerging multifaceted plant compounds. *Med. J. Aust.* **167**, 199–120.
Wattenberg, L. W., and Leong, J. L. (1970). Inhibition of the carcinogenic action on benzo(a)pyrene by flavones. *Cancer Res.* **30**, 1922–1925.
Wealth of India. (1991). *Wealth of India, a Dictionary of Indian Raw Materials and Industrial Products* Vol. **VII**. N-Pe Publication and Information Directorate CSIR, New Delhi.
Weiss, R. F. (1988). *Herbal Medicine. Translated from the 6th German edition of Lehrbuch der Phytotherapie by A. R. Meuss, FIL, MITI,*. pp. 37–52 Beaconsfield Publishers, Ltd., Beaconsfield, England.
Wichtl, M. (ed). (1994a). Nasturii Herba—Watercress (English translation by Norman Grainger Bisset). In *Herbal Drugs and Phyto-pharmaceuticals*, pp. 353–354. CRC Press, Stuttgart.
Wichtl, M. (ed). (1994b). Rhei radix—Turkish rhubarb root (English translation by Norman Grainger Bisset). In *Herbal Drugs and Phytopharmaceuticals*, pp. 415–418. CRC Press, Stuttgart.
World Health Organization (1989). World Health Organization Bulletin, 1989. *WHO Bull* **67**, 613–618.
Yagi, T., Yamauchi, K., and Kuwano, S. (1997). The synergistic purgative action of aloe-emodin anthrone and rhein anthrone in mice: synergism in large intestinal propulsion and water secretion. *J. Pharm. Pharmacol.* **49**, 22–25.
Yam, E. B. (1996). Diet and disease—the Israeli paradox: possible dangers of a high omega-6 polyunsaturated fatty acid diet. *Isr J. Med. Sci.* **32**, 1134–1143.
Yamamoto, I., Nagumo, T., Fujihara, M., Takahashi, M., and Ando, Y. (1977). Antitumor effects of seaweeds. 2. Fractionation and partial characterization of the polysaccharides with antitumor activity from *Sargassum fulvellum*. *Jpn J. Exp. Med.* **47**, 133–140.
Yamamoto, I., Nagumo, T., Yagi, K., Tominaga, H., and Aoki, M. (1974). Antitumor effects of seaweeds. 1. Antitumor effects of extracts from sargassum and laminaria. *Jpn J. Exp. Med.* **44**, 543–546.
Yamashita, K., Kawai, K., and Itakura, M. (1984). Effects of fructo-oligosaccharides on blood glucose and serum lipids in diabetic subjects. *Nutr. Res.* **4**, 961–966.
Yanagihara, K., Ito, A., Toge, T., and Numoto, M. (1993). Antiproliferative effects of isoflavones on human cancer cell lines established from the gastrointestinal tract. *Cancer Res.* **53**, 5815–5821.
Yang, C. S., Lee, M. J., Chen, L., and Yang, G. Y. (1997). Polyphenols as inhibitors of carcinogenesis. *Environ. Health Perspect.* **105** (4 Suppl), 971–976.
Yao, X. J., Wainberg, M. A., and Parniak, M. A. (1992).

Copyright © 2000 John Wiley & Sons, Ltd. 

Mechanism of inhibition of HIV-1 infection *in vitro* by purified extract of *Prunella vulgaris*. *Virology* **187**, 56–62.
Zava, D. T., Blen, M., and Duwe, G. (1997). Estrogenic activity of natural and synthetic estrogens in human breast cancer cells in culture. *Environ. Health Perspect.* **105** (3 Suppl), 637–645.
Zava, D. T., Dollbaum, C. M., and Blen, M. (1998). Estrogen and progestin bioactivity of foods, herbs and spices. *Proc. Soc. Exp. Biol. Med.* **217**, 369–378.
Zava, D. T., and Duwe, G. (1997). Estrogenic and antiproliferative properties of genistein and other flavonoids in human breast cancer cells *in vitro*. *Nutr. Cancer* **27**, 31–40.

Copyright © 2000 John Wiley & Sons, Ltd. 