Chinese medicine and biomodulation in cancer patients—Part two

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ABSTRACT

Traditional Chinese Medicine (TCM) is a whole system containing therapeutic interventions that individually induce biomodulation at the physiologic, chemical, and molecular levels. The theory of TCM proposes a synergy between specific interventions selected as part of a care plan based on TCM diagnostic theory. Combining TCM with the modern practice of oncology seems, in conjunction with biomedical interventions (surgery, radiotherapy, chemotherapy, and pharmaceuticals), to have potential advantages through the synergy of biomodulation. Biomodulation approaches are broadly categorized as modification of tumour response and reduction of adverse effects; modulation of immunity; prevention of cancer progression; and enhancement of symptom control. Although the database of preclinical studies is rapidly expanding, good-quality clinical trials are notably scarce.

Laboratory studies suggest that some herbs increase the effectiveness of conventional chemotherapy without increasing toxicity. A healthy immune system is necessary for control of malignant disease, and the immune suppression associated with cancer contributes to its progression. Many Chinese herbs contain glycoproteins and polysaccharides (among them, constituents of Coriolus versicolor, Ganoderma lucidum, Grifola frondosa, Astragalus membranaceus, Panax ginseng, and various other medicinal mushrooms) that can modulate metastatic potential and the innate immune system. Phytochemicals such as specific polysaccharides have been shown to boost the innate immune system, especially through interaction with Toll-like receptors in mucosa-associated lymphoid tissue. This intervention can potentially improve the effectiveness of new anticancer vaccines. An increase in virus-associated cancers presents a major public health problem that requires novel therapeutic strategies. A number of herbal therapies have both antiviral activity and the ability to promote immunity, possibly inhibiting the initiation and promotion of virus-associated cancers.

The mechanisms learned from basic science should be applied to clinical trials both of specific interventions and of whole-system care plans that safely combine the TCM approach with the conventional biomedical model. In Western medicine, the combination of TCM herbs with drug therapies is controversial, given lack of knowledge concerning whether a drug is favourably enhanced or whether adverse effects occur. Using initial data from the preclinical studies, future clinical research needs to evaluate the combinations, some of which are showing favourable synergy.

KEY WORDS

Chinese medicine, herbs, acupuncture, supportive care, immunity, research

1. INTRODUCTION

Biomodulation is the reactive or associative adjustment of the biochemical or cellular status of an organism. Most modulation events describe an interaction in which a molecule (modulating entity) alters the ability of an enzyme to catalyze a specific reaction. In the context of cancer, biomodulation includes the use of a substance to augment the host’s antitumour response, including immunotherapy. It encompasses the regulation of innate electrophysiologic, chemical, and molecular pathways through relatively low-intensity physical and chemical interventions. In contrast to conventional biomedicine—for example, pharmaceuticals—therapies such as herbs or their extracts are a mixture of chemicals administered at relatively low doses over a prolonged period of time. Acupuncture produces low-level electrochemical changes in the soft-tissue fascia. In TCM, the practice model includes the use of a diagnostic philosophy derived from cumulative clinical observation to target individual imbalances.

In Western medicine, the combination of TCM herbs with drug therapies is controversial, because of a lack of knowledge concerning whether the drug is favourably enhanced or whether adverse effects occur. Using initial data from preclinical studies, future clinical research has to evaluate the combinations, some of which are showing favourable synergy. Both parts of this article deal with examples of biomodulation and the results of combining TCM with biomedicine. Part one discussed
the broad principles of TCM; part two discusses the potential clinical applications of TCM in oncology.

2. ROLES OF TCM IN BIOMODULATION

The goals of cancer treatment should be to increase survival (when possible) and to improve quality of life for patients. Traditional Chinese Medicine is able to support patients being treated with conventional Western medicine (surgery, radiotherapy, and chemotherapy) through four approaches:

1. Modification of tumour response and reduction of adverse effects
2. Modulation of immunity
3. Prevention of cancer progression
4. Enhancement of symptom control

Very often, TCM therapy works through more than one approach synergistically.

2.1 Modification of Tumour Response and Reduction of Adverse Effects

2.1.1 Tumour Physiology

Evidence increasingly suggests that TCM can favourably modify the tumour response to conventional Western cancer treatment. There is a correspondence between the TCM theory of cancer and recent medical research findings. In TCM, the malignant tumour is viewed as being associated with stagnation of qi (energy) and blood. Qi may be viewed as a model for intracellular and intercellular information and potential energy transfer. That definition would correlate with the known abnormalities of signal transduction, cell contact, and electrophysiology of cancer cells.

Increased fluid content and a stagnant blood supply have been demonstrated in malignant tumours. The microcirculation within a tumour is very abnormal, and there are regions within the tumour where the blood flow is sluggish. In TCM, stagnation of blood is classically associated with tumours. The impaired blood circulation leads to areas of poor oxygenation in the tumour. Cancer cells that survive in an environment of low oxygen tension are also found to be more resistant to radiotherapy and to some types of chemotherapy. Interestingly, the use of anticoagulants such as heparin and coumadin (warfarin) as adjunctive treatment with chemotherapy has been shown in laboratory studies in animals to prevent the development of blood-borne metastases and in clinical studies to improve the survival of cancer patients. Destagnation or detoxification herbs are used to move the blood and qi within a malignant tumour. Many of these herbs are proving to be anti-angiogenic agents.

Herbs from TCM have been extensively investigated in the laboratory and are known to have multiple pharmacologic effects. Specifying the botanical parts from which the herbal agent is prepared is important, because the active pharmacologic agents depend on their source: “Radix” (Rx) denotes the root; “Cortex” (Cx), the bark or rind; and “Rhizome” (Rh), the rhizome. Many examples of anticancer therapeutic multiplicity are available:

- Rx Ginseng has antitumour activity and inhibits platelet aggregation and chemotherapy-induced immunosuppression.
- Glycyrrhizic acid has antitumour activity, acts as an anti-inflammatory by increasing serum cortisol, and also increases natural killer (NK) cell activity against cancer cells.
- Rx Astragalus membranaceus is a powerful stimulator of the immune system, has anti-tumour activity, and inhibits platelet aggregation.
- Rx Angelica sinesis stimulates the immune system, has antitumour activity, inhibits platelet aggregation, and inhibits vascular permeability.
- Rh Atractylodis macrocephala has antitumour activity and acts as an anti-thrombotic and fibrinolytic agent.
- Ginkgo biloba has multiple effects, including inhibition of platelet activation factor; stimulation of the immune system, fibrinolysis, and anti-thrombosis; scavenging of free radicals; and dilation of blood vessels to increase perfusion.

As more is learned about the interactive roles of bone marrow, hematopoietic system, and angiogenesis in the progression of cancer, the foregoing effects of herbs on the hemostatic coagulation system are interesting.

The possible usefulness of destagnation herbs was demonstrated in a randomized controlled clinical trial (RCT) evaluating the combined-modality treatment of a Chinese herbal destagnation formula and radiotherapy in patients with nasopharyngeal carcinoma. In that trial, 90 patients who received combined herbal and radiation treatment were compared with 98 patients who were randomized to receive radiation treatment alone. The ingredients of the herbal formula included Rx Astragalus membranaceus, Rx Paeoniae rubrae, Rx Ligustici chuanxiong, Rx Angelica sinesis, Semen persica, Flos Carthami tinctorii, Rx et Caulis jixueteng, Rx puerariae, Pericarpium citri reticulatae, and Rx Codonopsis pilosulae. As compared with the group treated with radiation alone, the combined-treatment group showed a statistically significant increase in local tumour control and overall 5-year survival. The rate of local recurrence in the intervention group was halved from 29% in those receiving radiation alone to 14% in the group receiving destagnation herbs as well. The 5-year disease-free survival was increased from 37% in the control group to 53% in the group receiving destagnation herbs.

It is postulated that the tested herbal destagnation formula may have improved tumour microcirculation and increased tumour blood flow, leading to an improvement
in the oxygen tension inside the tumour. Improved oxygen tension increases the radiosensitivity of the tumour. In other words, the destagnation formula acted as a radiation sensitizer.

In animal experiments, Ginkgo biloba was also shown to increase perfusion and radiosensitivity. Chinese herbs such as Salviae miltiorrhiza, which inhibits tumour edema caused by free radicals, may also increase tumour perfusion, oxygenation, and response to radiotherapy. Other herbs may directly sensitize neoplastic cells to radiotherapy.

Some herbs may protect normal tissues from radiotherapy. For example, Panax ginseng and Panax quinquefolium water extract (Rh2 ginsenoside) exercise radioprotection through mechanisms involving antioxidative and immunomodulating properties. The subtle balance between anticancer effects and protection of normal tissue—termed “therapeutic gain”—is not currently understood.

The TCM herbs contain a variety of chemicals that may act synergistically to inhibit tumour cell division, to increase tumour cell death (apoptosis), to increase the proportion of immune cells within the tumour, and to increase blood flow through the tumour. These changes are associated with a change in the balance of cytokines and other communicating peptides released by the immune cells, resulting in a reduction in the proliferation of tumour cells and an increase in tumour cell death, and in the minimization of many side effects for normal tissues. This synergy appears to be secondary to induction of apoptosis, anti-angiogenesis, antagonism of the viral genome, and induction of an immune response.

Some herbs can reverse multi-drug resistance. Extracts of multiple Chinese herbs traditionally used for anticancer therapy (for example, Anemarrhena asphodeloides, Artemisia argyi, Commiphora myrrha, Duchesnea indica, Gleditsia sinensis, Ligustrum lucidum, Rheum palmatum, Rubia cordifolia, Salvia chinensis, Scutellaria barbata, Uncaria rhynchophylla, and Vaccaria segetalis) demonstrate growth-inhibitory activity against various cancer cell lines, but limited inhibitory activity against normal cell proliferation. Huanglian (Coptidis rhizoma) induces cell-growth arrest and apoptosis by upregulation of interferon-β and tumour necrosis factor α (TGFβ) in human breast cancer cells.

Recent meta-analyses confirmed the utility of Chinese herbs both to enhance control of particular cancers (particularly viral-induced cancers such as hepatocellular carcinoma and nasopharyngeal cancers) and to reduce side effects of chemotherapy. Laboratory studies suggest that some herbs increase the effectiveness of conventional chemotherapy. For example, red ginseng acidic polysaccharide increases the cytotoxicity of paclitaxel, and Phellinus linteus enhances the cytotoxicity of doxorubicin. A meta-analysis of Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer indicates a promising therapeutic gain.

Occasionally, herbs alone are associated with tumour regression. For example, a 51-year-old woman with pathology-proven squamous cell carcinoma of the lung attained complete regression with the use of a combination of herbs as sole treatment (Herba Hedyotis diffusa, Rx Ophiopogonis, Herba Taraxaci, Rx Notoginseng, Pseudobulbus cremenae seu pleiones, Rx Panacis quinquefolii, Herba Houttuyniae, Bulbus Fritillariae thunbergii, Rh Pinelliae preparata). This anecdotal report is unusual, but deserves further exploration.

More clinical trials are required to further evaluate the promising role for herbs in potentially improving therapeutic gain.

2.1.2 Hormone Effects

Phytoestrogens that possess either estrogenic or antioestrogenic activity are found in some botanical supplements. Controversy has arisen concerning these substances for patients with hormone-responsive cancers who could theoretically deteriorate as a result of hormone-enhanced cancer progression. Angelica sinensis (dong quai), Glycyrrhiza glabra (liquorice), and the various ginsengs are cited in this category. However, in vitro and in vivo models of estrogenic activity have produced conflicting data. Clinically, the substances appear to serve as chemopreventive agents while also being capable of promoting growth in some estrogen receptor–positive cell lines. In addition, they may exert their estrogenic influence through either or both of receptor-dependent and receptor-independent mechanisms. Other studies demonstrate inhibition of breast cancer cell models, particularly by ginseng and its extracts. Pierson reviewed the conflicting data in detail.

Test-tube assays have limitations. They ignore issues related to metabolism and cannot address bioavailability. Phytoestrogens usually demonstrate higher activity in vitro than in vivo. In animals, route of administration and interspecies variability in metabolism produce unreliable results for the human situation. Human studies are confounded by the composition of gut flora, intestinal transit time, the redox potential of the colon, and genetic differences in metabolism. In addition, herbs are not single-entity drugs. Each is a complex mixture of hundreds of compounds that may exert their biologic activity alone or in synergy with other compounds, with multiple targets of action. Even if a phytoestrogen compound is present, other compounds may counteract its effect.

In vitro studies of Angelica sinensis show weak agonist activity on MCF-7 breast cancer cells, but human studies do not support an estrogenic mechanism of action. Indeed, although the proposed main utility of Angelica sinensis is to treat symptoms of menopause, a double-blind RCT showed no significant reduction in the relief of such symptoms, in endometrial thickness, or in vaginal maturation index.
The evidence for proestrogenic activity of the ginsengs against breast cancer is extremely weak and derives from two in vitro studies on MCF-7 cells. A study of 20(S)-protopanaxadiol, a major gastrointestinal metabolite of the ginsenosides, suggests that it inhibits estrogen-stimulated gene expression in MCF-7 estrogen receptor (ER)-positive breast cancer cells, inhibits xenograft growth, and enhances the cytotoxicity of tamoxifen in an ER-independent fashion. The Rh2 ginsenoside extract hypersensitizes multidrug-resistant breast cancer cells to paclitaxel. The tumoricidal effect of cisplatin on MCF-7 cells is not attenuated by American ginseng (Panax quinquefolius L.) 41. Water-extracted compounds of Panax quinquefolius L. inhibit MCF-7 cell proliferation by inhibiting mitogen-activated protein kinase. A combination herbal formula of ginseng and Carthami tinctorii inhibits a breast cancer cell line through apoptosis. Laboratory and epidemiologic data indicate that whole ginseng has anti-proliferative activity and a clinical study reported improvement in quality of life without increase in cancer recurrence. An abstract from the Mao Clinic (Rochester) presented at the 2007 American Society of Clinical Oncology meeting reported a phase II RCT of North American ginseng (Panax quinquefolium) for cancer patients suffering from fatigue, demonstrating an up to 40% reduction in fatigue in patients on the highest dose level. The cohort included breast cancer patients, and no adverse effects were reported. The safety aspects of ginseng in patients with hormone-responsive cancers are important because of emerging clinical evidence for the anti-fatigue and immunogenic properties of this herb.

The PC-SPES herbal combination has partial estrogenic activity associated with activity against prostate cancer. One study correlated laboratory activity with clinical response. On the basis of those findings, a U.S. National Cancer Institute (NCI) RCT was initiated. Unfortunately, the clinical trial was terminated when a batch of PC-SPES was found to be contaminated with the hormone diethylstilbestrol and other pharmacologic agents. It is not certain whether the contamination was accidental or the result of deliberate adulteration. However, there is evidence that the combination was more effective than diethylstilbestrol alone.

Soybeans contain genistein, which is an isoflavone with multiple anticancer effects demonstrated in the laboratory. These include the induction of tumour cell death through the process of apoptosis, inhibition of cancer cell proliferation by a decrease in the availability of sex hormones, inhibition of angiogenesis, inhibition of tyrosine kinase (involved in intracellular signalling from the membrane to the nucleus), and inhibition of platelet aggregation. Some epidemiology studies suggest that populations with a high soy or tofu content in their diet may have a reduced risk of breast cancer, other studies have not been able to confirm this link. Animal studies suggest that exposure to soy during early life may alter differentiation of breast cells in a way that protects them against later assault by carcinogenic agents. That finding would imply that soy protects against breast cancer only if regularly ingested before menarche. Some reports suggest that phytoestrogens contained within soy may reduce the symptoms of hot flashes associated with chemotherapy-induced menopause; however, most RCTs do not support that hypothesis. Practitioners should be cautious in treating patients with ER-positive breast cancer, especially those on estrogen antagonist therapy. The use of soy isoflavones to promote health in breast cancer survivors remains controversial because of scant scientific data.

Limited evidence suggests that acupuncture directly influences hormone levels. There is weak evidence that it modulates hormones such as melatonin and corticotrophin-releasing factor. Its effect is likely to occur via the central nervous system and the pineal and pituitary glands. A nonrandomized human study reported that acupuncture induced melatonin and was associated with improved sleep.

2.2 Modulation of Immunity

2.2.1 Herbs

Another strategy that TCM uses in cancer therapy is to strengthen the whole body–mind system by enhancing and harmonizing the energy balance between all the organs. This approach may be viewed as correcting an imbalance in the body–mind communication network—an intervention that is reflected in an enhancement in immunity. This “Fu Zheng” treatment is mediated by the specific group of TCM herbs called Fu Zheng herbs. There is some limited evidence that improvement in the immunologic function of cancer patients is associated with an improvement in their survival. In China, Fu Zheng herbs have been reported to increase survival when combined with radiotherapy for patients with nasopharyngeal cancer and when combined with chemotherapy for patients with stomach and liver cancer, but the clinical evidence is weak because of a lack of RCTs.

Fu Zheng herbs, including Rx ginseng, Ganoderma, Rx Astragalus membranaceus, Rx Angelica sinensis, Cordyceps sinensis, and Fructus Lycii, have been shown to enhance the body’s defence mechanisms. Clinical studies, including two randomized trials, have found that cell counts of NK cells and OKT4 (immune-enhancing) lymphocytes were increased with the use of Fu Zheng herbs. These immunocytes are known to attack cancer cells. In a study of gastric cancer patients, increased survival was found in the combined-treatment group (receiving both Fu Zheng herbs and chemotherapy) as compared with the chemotherapy-alone group.

Many of the Fu Zheng herbs are associated with an increase in cytokines, such as interferon and...
interleukin (IL)\textsuperscript{81–83}. Chinese studies also suggest that healing of normal tissues may be enhanced. Anti-inflammatory constituents may diminish radiation-induced ulcers and chemotherapy-induced stomatitis\textsuperscript{84,85}. These studies still need to be verified in the West, using acceptable standards and quality assurance.

Recently, the concept of immune enhancement gained new ground with the discovery that cytotoxic therapies and cancer both suppress immunity, and that low immune levels may increase the probability of relapse. In addition, an intact innate immune system is necessary for activity of the new cancer vaccines. The interaction of host immunity with the natural history of cancer is suggested by Burnet’s immune surveillance theory, by the fact that immunodeficiency diseases are associated with an increased risk of cancer, and by the fact that immune-enhancing therapies in malignant melanoma and renal cell carcinoma have produced antitumour responses. There is evidence that the healthy immune system is necessary for the control of malignant disease and that the immune suppression associated with cancer contributes to disease progression.

Natural immune mediators are implicated in resistance against tumour development\textsuperscript{86}. Adaptive immunity is often suppressed in tumour-bearing hosts, and specially designed agents are required to boost this defence\textsuperscript{87}. Hormonal manipulation of the host can result in the elevation of immune defences against cancer. Such manipulation strengthens both the adaptive and natural immune defences of the host, both of which play significant roles. Cytokines and hormones boost natural defence mechanisms during febrile reactions, which are now known as the acute-phase response. Hormonal stimulation of immune mechanisms, coupled with other immunostimulants, may be employed to good advantage for the combination immunotherapy of cancer.

Many Chinese herbs contain glycoproteins and polysaccharides that can modulate metastatic potential and the innate immune system. Metastasis of malignant tumours may be a specific receptor-mediated process in which organ-specific lectins play a role in the adhesion of disseminated tumour cells. Glycoprotein-mediated membrane identity is part of the human leucocyte antigen histocompatibility system. The abnormal carbohydrate group on the tumour cell could have formed during malignant transformation. The metastatic tumour cell, with its membrane-associated glycoprotein (often identical with the tumour marker) is recognized by organ-specific lectins as belonging to the organ, and is thereby captured. \textit{In vitro} experiments show that galactoglycoconjugates can inhibit the adhesion of tumour cells to hepatocytes\textsuperscript{88}.

Immune suppression in cancer contributes to progression and relapse\textsuperscript{86,89–97}. Multiple strategies for identifying candidate tumour antigens currently exist, and more is now understood about activation and regulation of immunity against cancer. Vaccines can target tumour-specific antigens, but adjuvants are required to boost the innate immune response, especially in patients who already have depressed immunity from tumour-derived signalling molecules and the effects of cytotoxic therapies\textsuperscript{98–100}.

Phytochemicals such as specific polysaccharides have been shown to boost the innate immune system, especially through interaction with Toll-like receptors (TLRs) in mucosa-associated lymphoid tissue (MALT)\textsuperscript{101–103}. The TLRs evolved to interact with polysaccharides found in the walls of bacteria; they are an essential part of developing and maintaining a competent immune system\textsuperscript{104}. Polysaccharide extracts and complexes from Chinese medicinal herbs and mushrooms may have a potential role in enhancing innate immunity. Clinical trials have provided some evidence that they can improve survival\textsuperscript{105}. The polysaccharide complexes and extracts include constituents of \textit{Coriolus versicolor} (whose extract is called Krestin, PSK, or PSP)\textsuperscript{106–118}, \textit{Ganoderma lucidum}\textsuperscript{119–121}, \textit{Grifola frondosa} (maitake MD-fraction)\textsuperscript{122–127}, \textit{Astragalus membranaceus}\textsuperscript{128}, \textit{Panax ginseng}\textsuperscript{129–132}, and various other medicinal mushrooms\textsuperscript{133–135}.

Molecular mechanisms for the immunobiologic functions may act through various receptors on macrophages, monocytes, and NK cells, which activate secretion of nuclear factor \(\kappa\)B and antitumour cytokines. Interactions may include complement receptor type 3, CD14, mannose, and beta-glucan receptors. There is evidence that polysaccharides derived from \textit{Astragalus membranaceus}, \textit{Acanthopanax senticosus} and \textit{koreanum}, \textit{Ganoderma lucidum}, and \textit{Platycodon grandiflorum}\textsuperscript{136,137} interact with TLRs (especially TLR4).

Regulatory T cells (Tregs) and myeloid suppressor cells inhibit the anticancer activity of NK and T-helper cells and are partly responsible for tumour progression, resistance to chemotherapy, and ineffective antitumour vaccines. Enhancement of innate immunity seems to improve anticancer therapies. Tregs are characterized by CD25 and FoxP3 expression. Their normal role is to control the adaptive immune response through cell contact–dependent mechanisms. The interplay between Tregs and antigen-responsive T cells is modulated by dendritic cells (DCs): whereas immature myeloid precursors of DCs suppress T-cell activation and induce Treg development, mature monocytes (macrophages) override Treg-mediated suppression. Mature DC macrophages can be activated through the TLR pattern-recognition receptors found on monocytes in the gastrointestinal tract. They then secrete IL-6, which renders T-helper and NK cells refractory to the suppressive effect of Tregs\textsuperscript{138}.

Other studies have shown that elimination of Tregs can significantly improve the outcome of cancer immunotherapy in preclinical models. For example, Sutmuller \textit{et al.}\textsuperscript{139} showed that therapeutic whole-cell vaccination against melanoma was significantly more effective upon depletion of CD4\textsuperscript{+}CD25\textsuperscript{+} Tregs with an anti-CD25 monoclonal antibody. Unfortunately,
they also showed that Treg depletion with anti-CD25 antibody carries an inherent risk of depleting tumour-specific effector CD4\(^+\) (and possibly CD8\(^+\)) T cells, thus negatively affecting treatment efficacy. Myeloid suppressor cells may have additional properties that can compromise anticancer therapies, such as promotion of angiogenesis\(^{140}\). Specific cytokines also play a role in immune suppression. The cytokines IL-13 and IL-4 suppress NK T cell immunosurveillance\(^ {141}\).

Tregs that suppress immune responses may limit the efficiency of cancer immunotherapy. Recent findings indicate that TLRs directly regulate the suppressive activity of Tregs. Linking TLR signalling to the functional control of Tregs may offer new opportunities to improve the outcome of cancer immunotherapy by co-administration of certain TLR ligands\(^ {142}\). Stimulation by TLR blocks the generation of DCs from progenitor cells and diverts them to mature macrophage monocytes. That effect is achieved by inhibition of granulocyte–macrophage colony–stimulating factor signalling through the induction of SOCS1.

Microbial ligands are able to skew the dichotomy of macrophage versus DC differentiation from common progenitors. In uninflamed tissues, granulocyte–macrophage colony–stimulating factor induces the generation of immature DCs, preparing the host to sense infectious danger. However, during infectious inflammation, TLR stimulation drives incoming monocytes to behave more like macrophages than to differentiate into DCs. That mechanism could be of help for the direct antimicrobial defence, which is more effectively mediated by macrophage-like cells with a high capacity to phagocytise. Pre-existing resident DCs are sufficient to perform the task of antigen sampling and transduction of information to the adaptive immune system. Thus, TLR stimulation would guide the innate immune system to assure a sufficient supply of phagocytic cells in inflamed tissues\(^ {143}\).

Garay\(^ {144}\) reviewed the potential benefits of TLR agonists when added to chemotherapy TLR2/4 agonists to induce well-controlled TNFα secretion at plasma levels known to make neoangiogenic tumour vessels permeable to the passage of cytotoxic drugs. Moreover, TLR2/4 agonists induce expression of inducible nitric oxide synthase, and nitric oxide is able to induce apoptosis of chemotherapy-resistant tumour cell clones. Finally, TLR2/4 stimulation activates dendritic cell traffic, macrophage production, and cytotoxic T-cell responses.

Breast cancer patients have increased levels of Tregs\(^ {145}\). Vaccine peptides need to be combined with strong adjuvants, such as TLR agonists. A peptide vaccination strategy that incorporates a TLR agonist could prevent the occurrence of spontaneous breast tumours. Transgenic mice that carry the activated rat epidermal growth factor receptor her2/neu oncogene were vaccinated with a synthetic peptide from the rat her2/neu gene product in combination with a TLR agonist adjuvant. The results show that, to obtain tumour antigen–specific T-lymphocyte responses and antitumour effects, the function of CD4/CD25 Tregs had to be blocked with anti-CD25 antibody therapy. Mice that were vaccinated using this approach remained tumour-free or were able to control spontaneous tumour growth; they also exhibited long-lasting T-lymphocyte responses. The results suggest that similar strategies should be followed for conducting clinical studies in patients\(^ {146}\).

The polysaccharide beta-glucans stimulate leukocyte anti-infective activity and enhance (murine) hematopoietic activity. In a study of human bone marrow mononuclear cells, PGG-glucan acted on committed myeloid progenitors to enhance activity by direct action independent of IL-3\(^ {147}\). Beta-glucans and polysaccharides are potent stimulators of TLR. Some specific polysaccharides have already been shown to boost the innate immune system through interaction with TLRs in MALT\(^ {101–103}\).

Polysaccharide extracts and complexes from Chinese medicinal herbs and mushrooms seem to have a potential role for enhancing innate immunity. There is some evidence from clinical trials that they can improve survival\(^ {105}\). Polysaccharide extracts from Panax ginseng can increase immunity and enhance chemotherapy\(^ {129–131}\). There is evidence of interaction with TLR, especially TLR4\(^ {136,137,148}\).

Maitake D-Fraction, a polysaccharide extracted from maitake mushrooms (Grifola frondosa), has been reported to exhibit an antitumour effect through activation of immunocompetent cells, including macrophages and T cells, with modulation of the balance between T-helper 1 and 2 cells. It can lower the dosage of mitomycin chemotherapy that is effective in tumour-bearing mice by increasing the proliferation, differentiation, and activation of immunocompetent cells\(^ {123}\).

Further evidence of the potential usefulness of polysaccharides in stimulating an enhanced immune response comes from a study of orally administrated beta-glucans (from maitake mushrooms) that demonstrated an enhancement of the antitumour effects of monoclonal antibody–targeted therapies\(^ {149}\). A meta-analysis of another immune-enhancing botanical, Astragalus, reported an enhancement of the efficacy of platinum-based chemotherapy for lung cancer\(^ {31}\) and PSK (Coriolus versicolor) for the enhancement of tegafur for colorectal cancer\(^ {108}\).

Immunosuppression in cancer patients can reduce the efficacy of anticancer vaccines and increase complications from opportunistic infections. Polysaccharides (mainly beta-D-glucans alone or linked to proteins) from the cell walls of various traditional Chinese medicinal mushrooms and plants show antitumour and anti-infective activities through activation of monocytes, macrophages, and NK cells. A future research strategy should authenticate the source of these polysaccharide extracts and screen them for interaction with TLRs in the gastrointestinal tract of animals. Oral agents that boost cell-mediated
immunity through MALT may be subsequently evaluated in human phase I studies for dose–response (cytokine and immune cell assays) and safety.

Optimized, authenticated polysaccharides may play a role in enhancing the potency of anticancer vaccines and other therapeutic modalities. These non-cytokine molecules appear to signal primarily through the TLRs, which are expressed by dendritic cells. In MALT, these agonists can induce a host of pro-inflammatory cytokines such as TNFα, IL-12, and IL-6, as well as CD4+ and CD8+ T cells.

Combining radiation therapy and TLR agonists may reduce the amount of radiation therapy required to eradicate tumours, with the TLR agonists thus acting as immunosensitizers. Evidence of the potential usefulness of polysaccharides in stimulating an enhanced immune response is strengthened by the study of orally administered beta-glucans (from maitake mushroom) that showed enhancement of the antitumour effects of targeted monoclonal antibodies. Ganopoly (a Ganoderma lucidum polysaccharide extract) modulated immune function in advanced-stage cancer patients. Treatment for 12 weeks resulted in a significant increase in the mean plasma concentrations of IL-2, IL-6, and interferon-γ, and a decrease in IL-1 and TNFα. Activity of NK cells increased, but no significant change was observed in terms of CD4+ or CD8+, or in the CD4+/CD8+ ratio.

Lymphoproliferative neoplasms, such as lymphomas and leukemias, may be particularly sensitive to changes in cytokine balance. The Memorial Sloan–Kettering Cancer Center in New York has commenced an NCI-sponsored phase I study of beta-glucan and rituximab in pediatric patients with relapsed or progressive CD20-positive lymphoma or leukemia. The evidence indicates that a healthy immune system is necessary for the control of malignant disease and that the immune suppression associated with cancer contributes to disease progression. Tumours have developed strategies to successfully evade the host immune system, and various molecular and cellular mechanisms responsible for tumour evasion have been identified. Some of these mechanisms target immune antitumour effector cells. Dysfunction and apoptosis of those cells in the tumour-bearing host creates an immune imbalance that cannot be corrected by targeted immunotherapies alone. Reversal of existing immune dysfunction and normalization of lymphocyte homeostasis in patients with cancer needs to be a part of future cancer immunotherapy. Therapeutic strategies are being designed to correct the immune imbalance, to deliver adequate in vivo stimulation, to transfer effector T cells capable of in vivo expansion, and to provide protection for the immune effector cells repopulating the host. Survival of these cells and long-term immune “memory” development in patients with malignancy are necessary for improving the clinical benefits of cancer immunotherapies. Polysaccharides derived from Chinese herbs and mushrooms are emerging agents that seem to enhance cytotoxic drugs, radiotherapy, surgery, and the newer targeted therapies and vaccines. Rigorous authentication and quality control of these phytoceuticals are necessary before clinical studies begin.

2.2.2 Acupuncture

Multiple animal and clinical studies have also suggested that acupuncture has a positive immune-modulating effect in cancer patients. In those studies, acupuncture has been shown to increase T-lymphocyte proliferation and NK cell activity, to activate the complement system and heat-stable mitogenic humoral factor, and to increase NK4 cell counts. Inhibition of the growth of transplanted mammary cancer has also been shown in mice with the use of acupuncture. The main acupoints that were used in these studies were those that support blood formation and spleen function. These points include L14, L111, St36, Sp6, Sp10, P6, UB20, GB39, and GV14. An increased level of all components (red blood cells, white blood cells, and platelets) was found.

Lu et al. recently reported an exploratory meta-analysis of the clinical trials. The trials from the Chinese journals suffered from low quality and biases. An analysis of a small set of seven trials did not find statistical significance in publication bias. The heterogeneity was explained by the varying treatment characteristics. The frequency of the acupuncture was once daily, with a median of 16 sessions. Use of acupuncture was associated with an increase in leukocytes during chemotherapy, with a weighted mean difference of 1221 cells/μL (95% confidence interval: 636 to 1807; p < 0.0001).

2.3 Prevention of Cancer Progression

In China, a high incidence of chronic viral infections results in cancers. Cancer sites include liver, stomach, esophagus, and nasopharynx. In addition, cervix cancer has increased to become the second most common cancer in women. The cause of the relatively higher incidence of virus-associated cancers as compared with the West is unclear. Factors include spread of infection, genetic predisposition, poor diet, and smoking. An inadequate response from the immune system to eradicate chronic viral infections and cancer cells is a common determinant. The total number of new cases of cancer was expected to increase by almost 15% by 2005. The increase in virus-associated cancers presents a major public health problem that requires more data directed at developing novel therapeutic strategies based upon local evidence-based remedies.

Hepatocellular carcinoma (HCC) is ranked second in cancer mortality in China, and the disease is now also increasing in frequency in men in many other countries. Hepatitis B (HBV) and C (HCV) viruses remain the major causative factors, and the hepatitis G virus and other transfusion-transmitted viruses cannot be
that dual infection with HBV and HCV is associated with a higher risk for HCC than is either infection alone, experiencing an increase in HPV-associated head and mission 178; however, a meta-analysis of existing meta-analysis concluded that HBV and HCV infections are important independent risk factors for HCC, and that dual infection with HBV and HCV is associated with a higher risk for HCC than is either infection alone, suggesting a synergism between the two 166.

Nasopharyngeal cancer is associated with Epstein–Barr virus infection 167,168. It may also be associated with some cases of Hodgkin lymphoma 169 and gastric cancer 170. Its highest incidence is in the Southern Chinese population, with familial aggregation. The annual detection rate is 433 per 100,000 for men and 499 per 100,000 for women in high-risk families, as compared with an average overall annual incidence in Hong Kong of 24 per 100,000 for men and 10 per 100,000 for women 171.

The incidence of cervix cancer is increasing. The combination of human papilloma virus (HPV) infection and cigarette-smoking is synergistic for the induction of cervix and anal cancers. In the West, the subtype HPV16 is the most common cause; in China, other types of HPV viruses (for example, HPV18 and 59) are more commonly associated with the disease. The HPV16 E7 variant protein may induce a host humoral immune response, but not a special cellular immune response 172. The association is strengthened in smokers. Inducing an appropriate cell-mediated immune response may be key to eradicating the virus and its potential to induce and promote cancer. The HPV16 virus is also a major factor in the development of esophageal cancer in China, but not yet in the West 173,174. In addition, the West and China are both experiencing an increase in HPV-associated head and neck cancers 175,176. Another major concern is a rise in breast cancer in women. Although a high-fat diet, less exercise, and reduced parity are contributing factors, infection with the HPV33 virus appears to play a role in China 177.

Most evidence for successful herbal treatment of cancers comes from case reports or case series that may be biased by selection or spontaneous remission 178; however, a meta-analysis of existing RCTs provided promising evidence that combining Chinese herbal medicine with chemotherapy may benefit patients with HCC 28. A major weakness of the data is that high-quality, rigorously controlled trials are lacking. Reasonable epidemiologic evidence suggests that Panax ginseng is a non-organ-specific cancer preventative, with a dose–response relationship 179. Ginseng extracts and synthetic derivatives should be examined for their preventive effect on various types of human cancers. A case–control study of green tea consumption and lung cancer in a population of women living in Shanghai showed an association with reduced risk in non-smoking women 180.

Some Chinese herbs increase immunity. Although Astragalus, Ligusticum, and Schizandrae have a long history of medicinal use within the TCM system, the West has only recently begun to understand their pharmacologic possibilities and clinical applications. Astragalus has demonstrated a wide range of immunopotentiating effects, and it has proven efficacious as an adjunct cancer therapy. Ligusticum and its active components have been investigated for enhancement of the immune system, treatment of ischemic disorders, and use as an anti-inflammatory. Clinically, the hepatoprotective and antioxidant actions of Schizandrae have proven beneficial in the treatment of chronic viral hepatitis 181. More data are required to determine the clinical effects of Chinese herbs on immunity and to prevent cancer progression 182.

The prevalence of AIDS is increasing rapidly 183, and research into the effectiveness of Chinese herbs on immunity may also help people with that syndrome. The syndrome is a result of infection with HIV, which subsequently leads to significant suppression of immune function. The search for effective therapies to treat AIDS is of paramount importance. Several chemical anti-HIV agents have been developed; however, besides high cost, adverse effects and limitations are associated with the use of chemotherapy for the treatment of HIV infection. Thus, herbal medicines have frequently been used as an alternative medical therapy by HIV-positive individuals and AIDS patients in China. For example, Scutellaria baicalensis georgi and its identified components (that is, baicalein and baicalin) have been shown to inhibit infectivity and replication of HIV 184. Some preliminary evidence of efficacy has recently been published 185.

Data from controlled clinical trials suggest that medicinal mushrooms may be beneficial as adjunctive anticancer therapies 120,186. A RCT in colorectal cancer patients receiving curative resection compared adjuvant chemotherapy alone to chemotherapy plus an extract (PSK) from the fungus Coriolus versicolor. Both disease-free and overall survival were significantly higher in the group that received the PSK 177. Medicinal mushrooms contain a class of polysaccharides known as beta-glucans that promote antitumour immunity. They may act synergistically with some of the new therapeutic antibodies and chemotherapy agents and may protect normal marrow 149,187. Maitake mushroom and Ganoderma lucidum are both Chinese medicinal mushrooms that are showing preliminary evidence that they can suppress viral infections and inhibit cancer progression through modulation of the immune system 124,188–190.

In TCM, appropriate nutrition according to specific constitutional and disease patterns is also emphasized. Green tea (Camellia sinensis) and Panax ginseng are two dietary supplements that have been extensively investigated in both laboratory and epidemiologic studies. Both reduce the risk of cancer induction, and they may prevent cancer recurrence 191–193. Green tea
contains isoflavones and a powerful antioxidant called epigallocatechin. The latter may potentiate the destruction of cancer cells by promoting apoptosis and inhibiting angiogenesis. \( \text{Panax ginseng} \) may induce the differentiation of neoplastic cells into normal tissue. Both epigallocatechin and ginseng restore normal intercellular communication through the gap junctions. Both dietary supplements work through novel mechanisms of signalling.

The isoflavones and phytoestrogens in soy appear to reduce the incidence of prostate cancer and may play a role in prevention and as adjunctive therapy to reduce the risk of recurrence. Cell culture and animal xenograft studies show that treatment with soy is associated with inhibition of prostate-specific antigen, deactivation of nuclear factor \( \kappa \) (a nuclear transcription factor), induction of apoptosis (programmed cell death), and inhibition of angiogenesis.

Future goals for cancer prevention in China include public education to reduce the risk of infection, mass immunization, antiviral drugs, and chemotherapy. These are extremely expensive programs, and more education and research are required before their implementation. However, many Chinese currently have access to traditional herbal remedies within the culture of TCM. Some of the herbs and their derivatives seem to be effective treatments. An opportunity exists to develop, refine, and evaluate the effectiveness of Chinese herbal medicine to prevent the development of cancers secondary to virus infections.

The idea of using Chinese herbs to prevent cancer progression is already being tested in the West. A TCM herb combination may reduce the risk of lung cancer in ex-smokers. An NCI-sponsored study being conducted through the BC Cancer Agency, led by Dr. Stephen Lam, is recruiting participants 45–74 years of age who are ex-smokers to evaluate the efficacy of a herbal combination called “anti-cancer preventive health agent” (ACAPHA). This compound contains \( \text{Sophora tonkinensis}, \ \text{Polygonum bistorta}, \ \text{Prunella vulgaris}, \ \text{Sonchus brachyotus}, \ \text{Dictamnus dasycarpus}, \ \text{and Dioscorea bulbifera}. \) In Chinese studies, ACAPHA reduced the risk of esophageal cancer by 50%, by reversing severe esophageal dysplasia. In addition, a pilot study of 20 former heavy smokers with bronchial dysplasia treated with ACAPHA showed that, after 6 months, 50% had complete regression of dysplasia, as compared with only 13% of subjects in the placebo group. \( \text{Panax quinquefolium} \) (American ginseng) appears to reduce death and increase quality of life in survivors of breast cancer, suggesting that some botanicals may prevent recurrence.

2.4 Symptom Control

Cancer patients experience multiple symptoms related either to the cancer itself or to late treatment side effects. Even if the cancer is cured, the survivor may still be suffering from the late treatment side effects, which have an adverse effect on quality of life and are often not effectively managed with conventional Western medicine. Chinese medicine plays a useful role in supportive care for these symptomatic cancer patients. Symptoms that can be effectively managed include general constitutional symptoms such as fatigue, depression, and pain, and specific symptoms such as gastrointestinal side effects and myelosuppression.

Cancer patients receiving chemotherapy usually develop myelosuppression (with risk of infection and bleeding) and gastrointestinal side effects (nausea, vomiting, and diarrhea). They easily become fatigued and develop a reduced appetite. In TCM terms, the chemotherapeutic agents are causing Spleen and Kidney deficiency, leading to a general decrease in \( \text{qi} \) and blood. Note that “Spleen” and “Kidney” refer to communication systems (resembling the acupuncture meridian system) rather than actual organs. Radiotherapy and chemotherapy act as “heat toxins” that damage \( \text{yin} \) and \( \text{qi} \). “Heart fire” is expressed as stomatitis; “deficient Spleen \( \text{qi} \)” is manifest as diarrhea. Chemotherapy drugs “disturb Spleen and Stomach \( \text{qi} \),” expressed physically as damage to the lining of the stomach and intestines.

The conventional oncologist will often find that the language of a TCM practitioner seems quite unusual and metaphoric, but that language is consistent within the TCM system of diagnosis and treatment. The physical expressions are only part of the disturbance in the body–mind network, and they will inevitably be accompanied by emotional disorders (such as depression, anxiety, insomnia) and constitutional change (such as fatigue or hyper-excitability and poor concentration). After an evaluation and diagnosis of the disturbance in the body–mind network, appropriate combinations of herbs, acupuncture, nutrition, and Qigong may be utilized.

2.4.1 Herbs

Gastrointestinal Toxicity, Depressed Immunity, and Fatigue: Chinese medicine treats the combination of gastrointestinal symptoms, depressed immunity, and fatigue as a single syndrome. Spleen and Stomach \( \text{qi} \) are supported by appropriate formulas containing Rx \( \text{ginseng}, \ \text{Poria}, \ \text{and Rh Atractylodis macrocephala} \). Ginger root has been shown in many clinical studies to have antiemetic activity. It appears particularly to help nausea that may be intransigent to standard antiemetics. Ginger syrup was shown in a recent study to be effective. Caution should be used in patients on anticoagulants or those with low platelet levels, because the syrup has anticoagulant effects at higher doses.

Depleted \( \text{yin} \) leads to dry and sore mouth, thirst, constipation, and scanty dark urine. The harmonious relationship between Kidney and Heart is disturbed, leading to insomnia, restlessness, disorientation, palpitations, and low back pain. This combination of symptoms is traditionally alleviated with combinations
of Rh Anemarrhenae, Cx Phellodendron, and Rx Rehmanniae.

Vitexina (Vigna radiata) is a flavonoid herb with radioprotective effects that may be useful for reducing some side effects of radiotherapy. It treats the heat (yin)–deficiency side effects of anticancer treatment, such as fatigue, restlessness, insomnia, and constipation. This “empty heat” syndrome is characterized through tongue diagnosis, which reveals a red, denuded, and cracked tongue. Because the tongue is the most densely innervated organ in the body, it may reflect the imbalance between yin and yang via the autonomic nervous system, which in turn may influence blood flow and epithelial cell turnover through the local release of neuropeptides and cytokines. A RCT of breast cancer patients receiving radiotherapy showed that vitexina prevented the “empty heat” syndrome, reduced weight loss, and protected against a reduction in peripheral lymphocytes and platelets.215

According to Chinese medicine, the weakening of qi is associated with depressed immunity and susceptibility to infection and cancer progression. Medicinal mushrooms such as Ganoderma, Cordyceps sinensis, and Shiitake strengthen the qi, which is associated with an improved immune profile and antitumour activity. Another herb with potent immune-stimulating properties is Rx Astragalus membranaceus. In Western terminology, these patients are fatigued and have depressed immunity that renders them more susceptible to infection. High-quality clinical studies are rare, but the Mao Clinic (Rochester) recently reported a promising phase II RCT of ginseng (Panax quinquefolia L.) for fatigue in cancer patients. They reported a dose–response and demonstrated a 40% reduction in fatigue for patients taking the highest dose level as compared with those taking placebo.49

At least five RCTs have shown that Chinese herbal treatment can decrease the degree of myelosuppression, reduce gastrointestinal side effects, and increase appetite.39,68–71,73–78,80,216 Importantantly, such treatment can also increase the probability of completion of scheduled chemotherapy. One randomized trial recruited 669 patients with late-stage gastric cancer.74 One group of patients was treated with herbs that support Spleen and Kidney function (“jian pi yi shen prescription”) twice daily for 4–6 weeks with concurrent chemotherapy; another group was treated with the same type of chemotherapy alone. The combined-treatment group showed significantly higher leukocyte and platelet counts with fewer general and gastrointestinal side effects. The percentage of patients completing the scheduled chemotherapy was 95% in the combined-treatment group as compared with 74% in the chemotherapy-alone group (a statistically significant result at the 0.01 level). Unfortunately, the quality and verification of the data from these studies, which were reported from China, are not at a high enough standard that a definitive meta-analysis can be undertaken at this stage.

A more recent high-quality study was reported from Hong Kong.217 This double-blind placebo-controlled RCT used Chinese herbal medicine for the reduction of chemotherapy-induced toxicity from adjuvant therapy for breast or colon cancer. The herbal combination was individualized by the TCM practitioner and then randomized against placebo. The investigators could not show a reduction in hematologic toxicity, but they reported a significant impact on control of nausea.

The role of Chinese herbs in combination with conventional Western pharmaceuticals for symptom control is currently unclear. Laboratory data suggest that herbs can be effective modifiers of biochemical pathways, immunostimulants, and signal transduction modulators. But detrimental interactions and idiosyncratic toxicity are certainly a potential possibility.

A Cochrane systematic review of Chinese medicinal herbs for chemotherapy side effects in colorectal cancer patients found some merit in the concoction termed “huangqi compounds” (containing Astragalus).22 Four relevant trials were reviewed, all of low quality. None of the studies reported common toxicity criteria. There appeared to be a significant reduction in the number of patients who experienced nausea and vomiting, a decrease in the rate of leucopenia, and an increase in T-lymphocyte subsets. Although no adverse effects were reported, these are rarely documented in Chinese studies. Another Cochrane systematic review of Chinese medicinal herbs used to treat the side effects of chemotherapy in breast cancer patients provided limited evidence, although benefits in bone marrow improvement and quality of life were suggested.218 Future studies using more rigorous methodology and quality assurance are required.

Chemotherapy and Radiotherapy-Induced Cognitive Dysfunction: Chinese herbal therapies may have a role in improving cognitive function. Because conventional pharmaceutical interventions have produced very limited improvement, opportunities are opening to investigate some natural health products from the Chinese pharmacopoeia.

Many patients complain about changes in cognitive function during and after chemotherapy. This phenomenon has been particularly studied in breast cancer patients.219,220 Despite the fact that neurocognitive deficits limit productivity and independence for patients, these problems are underreported by patients and underdiagnosed by health care professionals. At least 18% of cancer patients who received standard-dose chemotherapy manifested cognitive deficits on post-treatment neuropsychological testing, and that effect may be sustained 2 years after treatment.221 The patients typically complain of a “foggy brain.” The impairments have an impact on tests that require sustained attention and speed of information processing. Fatigue and depression are associated disorders. Whether the initial cause of dysfunction is attributable to loss of neuronal integrity or is secondary to a
metabolic pathology is as yet unknown. There may be a genetic component, such as the e4 allele of Apolipoprotein.

Because “chemo-brain” is mainly a subjective phenomenon, it is important to develop techniques to objectively measure neurophysiologic or anatomic changes. Cytokines such as IL-1 and interferons may play a role, according to some animal experiments. Chemotherapy may damage the endothelium of blood vessels, resulting in thromboses and micro-infarcts in the central nervous system. Currently, the changes that occur in cerebral tissue after anticancer treatments are poorly understood, and no proven interventions are available.

Radiotherapy treatment of the brain can also impair cognitive function. Long-term survivors experience major cognitive dysfunction that influences their rehabilitation and quality of life. Radiotherapy can damage the brain, eventually resulting in demyelination that may appear only months later and lead to the development of cognitive impairment. These deficits manifest as any or all of impaired memory; diminished attention; lowered concentration; or functional, behavioural, and psychiatric deficits; and similarities to Alzheimer disease are seen. Receptors for N-methyl-D-aspartate (NMDA) are overactivated, leading to neuronal damage and learning impairment.

Interventions that could ameliorate such disabilities would be of great benefit to these patients and their caregivers. Ginkgo biloba, from the ginkgo tree, has a long history of use in TCM. Effects of Ginkgo biloba extracts have been postulated to include improvement of memory, increased blood circulation, and beneficial effects to patients with Alzheimer disease. The most unique components of the extracts are the terpene trilactones—that is, ginkgolides and bilobalide. These structurally complex molecules have been attractive targets for total synthesis. Terpene trilactones are believed to be partly responsible for the neuromodulatory properties of Ginkgo biloba extracts, and several biologic effects of the terpene trilactones have been discovered in recent years, making them attractive pharmacologic tools that could provide insight into the effects of Ginkgo biloba extracts.

Ginkgolides A, B, C, J, K, L, and M and bilobalide are rare terpene trilactones that have been isolated from leaves and root bark of the Chinese Ginkgo biloba tree. The compounds were found to be potent and selective antagonists of platelet-activating factor, responsible for their effect of increasing bleeding time. The mean absolute bioavailability for ginkgolides A and B and bilobalide are 80%, 88%, and 79% respectively. Much of the given dose is excreted unchanged in urine. Radioactive isotope studies show cerebral availability, particularly in the hippocampus, striatum, and hypothalamus.

Lipid peroxidation and brain edema are important factors that produce tissue damage in head injury. An investigation of the effect of mexiletine and Ginkgo biloba extract (EGb 761) on head trauma in rats showed the usefulness of mexiletine and its combination with EGb 761 as a cerebroprotective agent. In vivo studies have indicated that systemically administered bilobalide, a sesquiterpene trilactone constituent of Ginkgo biloba leaf extracts, can reduce cerebral edema produced by triethylin, decrease cortical infarct volume in certain stroke models, and reduce cerebral ischemia. In vitro and ex vivo studies indicate that bilobalide has multiple mechanisms of action that may be associated with neuroprotection, including its preservation of mitochondrial ATP synthesis, its inhibition of apoptotic damage induced by staurosporine or by serum-free medium, its suppression of hypoxia-induced membrane deterioration in the brain, and its action in increasing the expression of the mitochondrial DNA-encoded COX III subunit of cytochrome C oxidase and the ND1 subunit of NADH dehydrogenase. Because multiple modes of action may apply to bilobalide, it could be useful in developing therapy for disorders involving cerebral ischemia and neurodegeneration.

Standardized ginkgo leaf extracts such as Eggb761, 120–720 mg daily, have been used in clinical trials for dementia, memory, and circulatory disorders. A common dose is 80 mg or 240 mg (divided into 2 or 3 doses) daily of 50:1 standardized leaf extract by mouth. Ginkgo biloba increases vascular perfusion and improves cognitive function. It also protects damaged neurons by maintaining the balance of inhibitory and excitatory amino acids and inhibiting the effect of glutamate on the NMDA receptor. Some RCTs and a Cochrane review concluded that its use is promising; however, other RCTs have not confirmed its effectiveness. That ineffectiveness may be a function of inadequate dose or purity of the preparation.

When compared with cholinesterase inhibitors, Ginkgo biloba is better tolerated with similar efficacy. An abstract from Wake Forest University described a phase II (non-controlled) study in brain-irradiated patients and concluded that Ginkgo biloba can improve cognitive dysfunction. A dose of 40 mg 3 times daily was administered for 30 weeks. Of 34 patients entered into the study, 18 completed the 30 weeks of treatment; 16 patients went off-study because of tumour progression, treatment toxicity, or choice to discontinue treatment. Brain quality of life as measured by the Functional Assessment of Cancer Therapy–Brain Subscale was significantly improved at 12, 24, and 30 weeks as compared to baseline. Mood improved on the Profile of Mood States scale, confusion and fatigue were reduced, and cognitive testing showed improved attention and executive function. A RCT to compare donepezil with Ginkgo biloba (Eggb761) is currently being initiated at Wake Forest University.

Hasegawa reviewed the metabolism of individual ginsenosides. Ingested ginsenosides are metabolized in the large intestine through deglycosylation.
by colonic bacteria followed by fatty acid esterification. The resulting metabolites enter the circulation, where they exert their pharmacologic effects. The ginsenosides can inhibit NMDA receptor-mediated signals $250–254$. A combination of ginseng and *Ginkgo biloba* was shown to improve cognitive function in normal volunteers $255$. Laboratory studies suggest that inhibition of the neurotoxic effects of NMDA receptor overactivity by ginseng derivatives may delay or reverse neurocognitive dysfunction, but as yet, no controlled clinical studies have addressed that hypothesis. However, one type of ginseng (*Panax quinquefolium*) has demonstrated encouraging therapeutic effects in a clinical trial involving memory deficiency $256$. Ginseng derivatives and *Ginkgo biloba* both inhibit the overstimulation of the NMDA receptor by glutamate, which is implicated in neurodegenerative disorders. Ginsenosides may also increase cerebral acetylcholine levels. Although it is not yet known whether radiotherapy specifically interacts with the NMDA receptor or acetylcholine levels, the clinical and pathologic process appears similar to primary and vascular dementia alike $257$. Animal and early clinical evidence suggests that *Ginkgo biloba* and ginseng derivatives could have a neuroprotective effect, reducing cognitive impairment.

### 2.4.2 Acupuncture

**Emesis:** Acupuncture treatment at acupoint P6 has been shown to increase the antiemetic effect of drugs for perioperative and chemotherapy-induced nausea and vomiting $258,259$. Innovative single-blind RCTs have since confirmed these results $260–262$ and led to a consensus statement from the U.S. National Institutes of Health that “acupuncture is a proven effective treatment modality for nausea and vomiting” $263$. A three-arm RCT comparing conventional modern antiemetics (such as the 5-hydroxytryptamine 3 receptor antagonists), electroacupuncture, and the combination of antiemetic drugs and acupuncture clearly demonstrated that the combination arm was the most effective for preventing nausea and vomiting $264$. Stimulation of P6 may be carried out more conveniently with a small transcutaneous nerve stimulation (TENS) device, such as the ReliefBand (Neurowave Medical, Chicago, IL, U.S.A.). However, a recent RCT could not confirm the efficacy of TENS in the control of chemotherapy-induced nausea in women with breast cancer $265$, despite promising results in patients with motion sickness. Those results may be attributable to the focus on nausea rather than vomiting, to physiologic tolerance, or to maximal control having already been reached by the application of pharmaceutical antiemetics in these patients such that the device provided no advantage over medication alone. A meta-analysis of acupuncture-point stimulation for chemotherapy-induced nausea or vomiting shows a benefit over and above drug therapy $266$; however, the studies did not all use optimal drug therapy, and the pharmaceutical approach may need to be optimized before acupuncture is used in refractory cases. According to the meta-analysis, self-administered acupressure also appears to have a protective effect against acute nausea.

**Pain:** Pain is a common symptom of cancer. The causes of the pain can be the cancer itself or its treatment. Acupuncture, along with other interventions, has been shown to be effective in managing pain and other symptoms in cancer patients $267$. In a retrospective study from the Royal Marsden Hospital in London, England, 183 cancer patients with malignant pain, iatrogenic pain, and radiation-induced chronic ulcers were treated with acupuncture $268–270$. An improvement was seen in 82% of the patients, but effectiveness lasted for more than 3 days in only half of the patients. Iatrogenic pain (for example, pain resulting from radiation fibrosis or skin ulceration) and pain caused by secondary muscle spasm responded better than did malignant pain. Furthermore, increased blood flow, with improved healing of skin ulcers, was demonstrated after treatment with acupuncture. A RCT using ear acupuncture showed a profound effect on cancer pain $271$, and we obtained encouraging results from a small pilot study of acupuncture for chemotherapy-induced neuropathic pain $272$. A systematic review could not demonstrate the effectiveness of acupuncture as an adjunctive analgesic method for cancer patients $273$; however, it included only one RCT $271$, and all the other studies were generally of poor scientific quality. The intensity of stimulation, especially electrostimulation, may be important $274$.

We suggest that acupuncture is a useful treatment modality that may best be combined with other treatments to improve pain control, resulting in reduced doses of pharmaceutical analgesics. The reduction in medication use has the benefit of reducing the incidence and degree of drug-induced side effects. For some patients, a TENS device has the advantage of easy self-administration or administration by staff after minimal training.

Acupuncture-like TENS (AL-TENS) devices have been developed to apply low-frequency (4 Hz, for instance), high-intensity stimulation that mimics acupuncture treatment $275$. The goal is to recruit the high-threshold type III afferent nerve fibres that are potent releasers of endorphins. Recent meta-analyses (including a Cochrane systematic review) have shown that AL-TENS is more effective than placebo and improves function more than standard TENS in the treatment of chronic pain $276–279$. The AL-TENS devices are very simple machines that patients can learn to operate with less than 60 minutes of training. An acupuncture prescription may then be given to the patient, who can administer the appropriate treatments with AL-TENS at home. The Codetron (EHM Rehabilitation Technologies, Toronto, ON, Canada) is a sophisticated AL-TENS device that has the advantage of reducing tolerance to its analgesic effect by electronically rotating through a series of random electrical stimulation patterns and acupoint locations.
Xerostomia: Radiation-induced xerostomia is one of the distressing late side effects seen in patients who receive radiation treatment involving the parotid glands. The condition leads to loss of taste and difficulty in speaking and swallowing for the patients. Recently, acupuncture treatment has been found to increase blood flow to the parotid glands and may stimulate tissue regeneration in glands damaged by radiotherapy.\(^{280–282}\)

A RCT involving 38 patients with radiation xerostomia was reported from the Karolinska Institute in Sweden.\(^{283}\) Subjects were randomized to either deep acupuncture treatment or superficial acupuncture treatment. The superficial group was used as the control, despite previous evidence that superficial acupuncture treatment can have a certain degree of effectiveness and should not be used as a control in acupuncture treatment trials. In the Swedish study, more than 50% of the patients in both groups were found to have experienced a greater than a 20% increase in saliva flow rate. In the deep acupuncture group, 68% of patients demonstrated an increase in salivary flow rate. Changes in the control group were smaller and appeared after a longer latency phase. Moreover, patients in the treatment group reported less dryness, less hoarseness, and improved taste.

In another study, 70 patients with xerostomia attributable either to Sjögren syndrome or to irradiation were treated with acupuncture.\(^{284}\) A statistically significant increase in unstimulated and stimulated salivary flow rates was found in all patients immediately after acupuncture treatment, and for up to 6 months of follow-up. After a review at 3 years, patients who chose to be treated with additional acupuncture demonstrated a consistently higher median salivary flow rate as compared with patients not choosing to have additional acupuncture.

Despite some limitations in design, both of the foregoing studies provided evidence suggesting that acupuncture can be effective in treating radiation-induced xerostomia, with minimal side effects. In a prospective single-cohort visual-analogue-assessed study of acupuncture in palliative care patients with xerostomia, highly significant alleviation of subjective xerostomia was observed.\(^{285}\) Other studies are confirming the clinical use of acupuncture for relief of radiation-induced xerostomia.\(^{286}\)

At the Juravinski Cancer Centre in Ontario, Canada, a combined phase I and II study of AL-TENS in the treatment of radiation-induced xerostomia was carried out.\(^{287}\) The 45 participating patients were randomized into three treatment groups that received Codetron AL-TENS stimulation to one of three different sets of acupuncture points:

- Group A: CV24, St36, Sp6, LI4
- Group B: CV24, St36, Sp6, P6
- Group C: CV24, St5, St6, Sp6, P6

The goal of the study was to determine the optimum pattern of stimulation (based on TCM theory) to feed into the design of a placebo-controlled study. The AL-TENS treatment was administered twice weekly for a total of 12 weeks. Unstimulated and stimulated salivary flow rates before, during, and after treatment were measured, and the patients’ quality of life was surveyed at a 1-year follow-up. Improvement in xerostomia symptoms was noted, with mean score increases of 86 (\(p < 0.0005\)) and 77 (\(p < 0.0001\)) on the visual analogue scale at 3 and 6 months respectively after treatment completion. For all patients, the increase in mean basal and citric acid–primed whole saliva production at 3 and 6 months after treatment completion was also statistically significant (\(p < 0.001\) and \(p < 0.0001\) respectively). No statistically significant change in the quality-of-life evaluation as compared with baseline was observed.

Those results suggest that Codetron treatment improves saliva production and related symptoms in patients suffering from radiation-induced xerostomia. Treatment effects are sustained at least 6 months after completion of treatment. A recent study using functional magnetic resonance imaging showed activation of the insula region of the brain, the location associated with gustatory function.\(^{288}\)

Anxiety, Depression, Cognitive Impairment, and Fatigue: Suppression of anxiety by acupuncture is associated with an increase in the pain threshold. Acupuncture can also play a role in the treatment of fatigue and malignant cachexia through the modulation of cytokines and hormones.\(^{290–295}\)

Treatment of depression is an important intervention in the management of the body–mind network in cancer patients. Conventionally, clinical depression is treated with oral medication such as amitriptyline or the newer serotonin reuptake inhibitor drugs. Studies indicate that acupuncture treatment may be an equally effective alternative modality to drug treatment in patients suffering from mild depression. In one study, the side effects profile associated with acupuncture treatment was shown to be better than that associated with amitriptyline. In a single-blind placebo-controlled study of the antidepressant mianserin, supplementary acupuncture improved the course of depression more than did pharmacologic treatment with the drug alone.\(^{297}\)

A Cochrane review concluded that the evidence is insufficient to determine the efficacy of acupuncture as compared with medication or with wait list control or sham acupuncture in the management of depression; however, because pharmaceutical antidepressants are not usually effective until 2 weeks after the start of therapy, their combination with acupuncture may produce more rapid results with reduced side effects.

The role of acupuncture for cognitive impairment caused by chemotherapy or radiotherapy is unclear. An intriguing study in rats showed improvement in cognitive impairment caused by multiple infarcts. A recent review concluded that some limited evidence supports the
use of acupuncture in effectively managing a range of psychoneurologic problems, some of which are similar to those experienced by patients with chemotherapy-associated cognitive dysfunction. A phase II study of acupuncture for post-chemotherapy fatigue (average of 2 years) showed a mean improvement of 30% on the Brief Fatigue Inventory. That finding met the research group’s pre-specified criterion of clinical importance and has prompted initiation of a sham acupuncture RCT.

Miscellaneous Symptoms: Other symptoms that may be helped with acupuncture include constipation, trismus (post-radiotherapy contracture of the masseter muscle), radiotherapy-associated proctitis, hiccupps, persistent yawning, chemotherapy-induced peripheral neuropathy, and dysphagia secondary to an esophageal neoplasm. Although observational studies by Filshie et al. showed that acupuncture may improve cancer-associated dyspnea, that group’s findings were not supported by a later RCT using semi-permanent acupuncture studs.

Acupuncture can reduce the hot flushes associated with anticancer hormone therapy. Three prospective uncontrolled cohort studies have been completed, one in men who had undergone castration for prostate cancer, and two in women who were taking tamoxifen for breast cancer. All demonstrated a reduction in vasomotor symptoms. Prolonged stimulation using semi-permanent studs or needles, especially at SP6 appears to be associated with more long-term relief of symptoms.

3. CONCLUSIONS

Emerging scientific evidence suggests that TCM can play an important role in the supportive care of cancer patients. Enough preliminary evidence is available to encourage good-quality clinical trials evaluating the efficacy of integrating TCM into Western cancer care. Currently, the evidence for the utility of TCM in cancer care is promising, but prospective RCTs for specific clinical scenarios are necessary to obtain reliable and generalizable data.

Appropriate stratification and individualization according to TCM diagnostic criteria is possible within the context of a RCT. We believe that an evidence-based approach can be integrated into an individualized therapeutic plan and that a major role still exists for individual belief systems and psycho-spiritual experience. Assessment and measurement of coping strategies, maintenance of function, quality of life, and patient satisfaction are important. We are hopeful that future integration of various models of health such as TCM may lead to further improvements in survival and quality of life for cancer patients.

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5. REFERENCES


CHINESE MEDICINE AND BIOMODULATION IN CANCER PATIENTS


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For in-depth information, readers may want to visit these linked sites:
Society for Integrative Oncology (SIO)
Shanghai International Symposium: Integrative Oncology Theory, Research, and Practice April 25–26, 2008, Shanghai, China
and
Society for Integrative Oncology