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# Ancient Remedies and Modern Anticancer Therapies

## Rediscovering Traditional Chinese Medicine

One of the earliest records of description on tumours is the note of “nodules and lumps” by doctors in China during the Qin Dynasty (221-207 BC). Traditional Chinese Medicine (TCM) encompasses a range of early medical practices and remains widely used by healthcare professionals not only in China, but throughout Asia, Europe and America. As a part of the today’s complementary and alternative medicine (CAM), TCM has been widely accepted, at least in China and the Far East, as a therapeutic approach in the management of malignancies, particularly in the supportive and palliative care of cancer patients. TCM still seems to be mystical in some ways, and is often seen as less convincing due perhaps to the poor scientific understanding of its pharmacodynamics, mechanisms of action, and unconvincing clinical evidence by today’s standards and theory of medical science. However, in 2007 alone, \$33.9 million was spent by adults in the USA on CAM [1], and *Nature* published in 2011 a series of correspondence about traditional Asian medicine. These have raised an interest in assessing the potential use of traditional Asian medicine in cancer management and in attempting to elucidate the mode(s) of actions of these traditional therapeutic approaches. Since the middle of the last century, clinicians and scientists have intensified their search for more effective anti-cancer therapies by looking into TCM, particularly the natural herbs used in this area. This has led to successes in the rediscovery of certain TCM therapies by providing supportive scientific and clinical evidence. For example, Icariside II, purified from the root of *Epimediumkoreanum* Nakai can induce apoptosis in human acute myeloid leukemia (AML) cells (U937) through the STAT3 pathway [2]. Another natural compound, Artemisinin, extracted from the Chinese medical herb *Qinhao*, has been widely used in the treatment of malaria and cancer [3-6]. Investigations of certain herbal medicines have reached clinical trials examining their efficacy and safety in cancer management that is based on sound evidence from well-designed clinical studies.

### Adjuvant anti-cancer therapies

To date, surgery, chemo- and radio-therapies remain the cornerstones of the treatment for most solid tumours. Side effects and toxicity of chemotherapy and radiotherapy often restrict their application and effectiveness. Indeed, patients who undergo long term chemo- and radio- therapy may have to forego these treatments because of the accompanying toxicity and other side effects. A case can be made for TCM to enhance the responses to chemo- and radio-therapeutics and reduce the severity of these side effects due to conventional treatments. It can help improve quality of life and survival of cancer patients [7]. A number of herbal medicines seem to be beneficial to cancer patients, including single herb traditional herbal formulations and preparations of Chinese medicine. The following are some recent examples. The former includes *Radix Astragali* (Huang Qi), *Ginseng* (Ren Shen), *Mylabris* (Ban Mao), *Toad venom* (Chan Su), *garlic* (Da Suan) and *Turmeric* (Jiang Huang). *Mylabris*, in particular, can induce apoptosis of cancer cells and bolster the immune system. Its clinical application is nonetheless restricted due to renal toxicity and bone marrow suppression. On the other hand, *Astragalus* has a potential immunomodulatory role in combination with chemo- and radio-therapies by increasing the activity of lymphocytes, natural killer cells and macrophages, thereby leading to the secretion of interferon (IFN), interleukin 6 (IL6) and tumour necrosis factor (TNF). It can also enhance the biological function of IL2, and simultaneously reduce its adverse effect [8,9]. A TCM formula, *YangzhengXiaoji* (YZXJ), which consists of 16 herbs including *Radix Astragali*, *Ginseng*, *atractylodesmacrocephaloidz*, *poriacocosetc* (Table 1) has an anti-cancer action [10]. In a randomised double-blind trial in patients with lung cancers, conventional chemotherapy combined with YZXJ (n=304) showed significant disease remission (complete and partial remissions) compared with patients who received chemotherapy alone (n=103) (23.3% vs 14%, respectively,  $p < 0.01$ ) [10]. The patients who received YZXJ also had less bone marrow suppression. YZXJ has been used in treating liver,

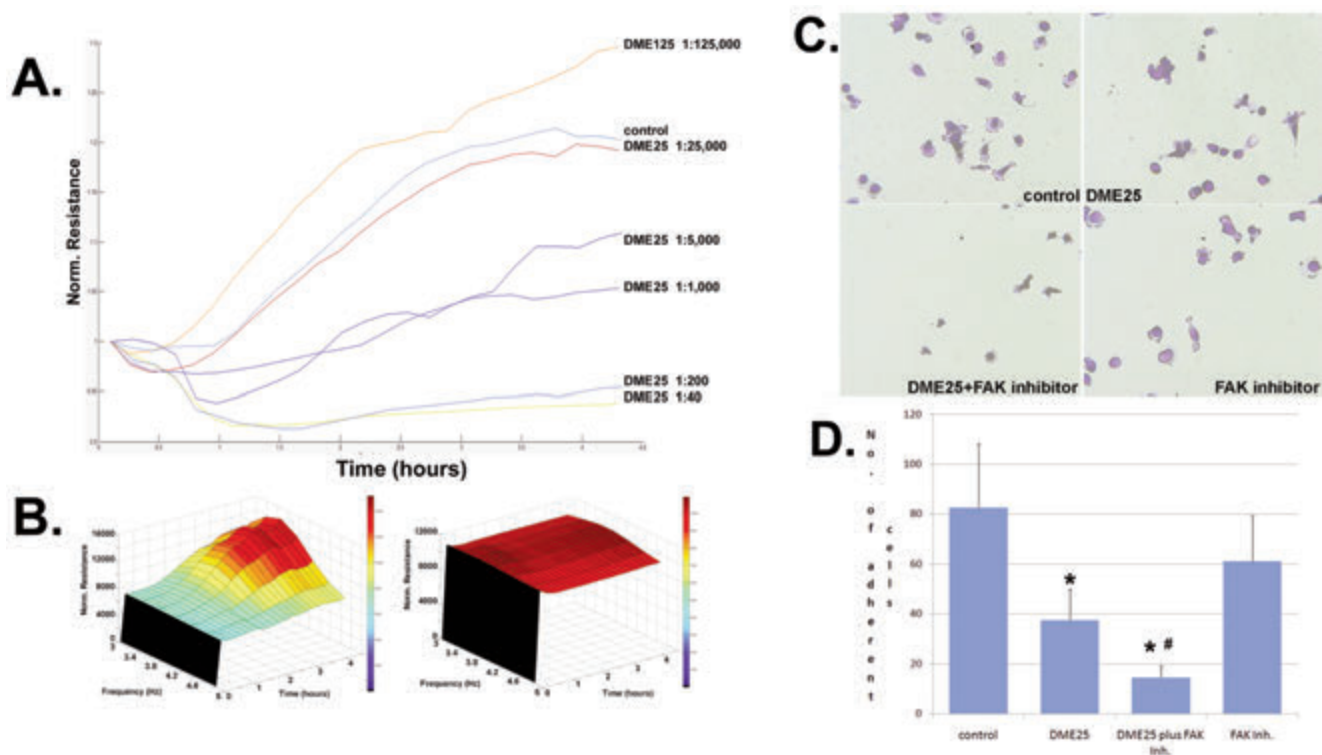


Figure 1. YZXJ (DME25) inhibition of the adhesion of vascular endothelial cell (HECV) to the extracellular matrix, enhanced by FAK inhibitor. A and B: Concentration dependent inhibition of the matrix adhesion of HECV cells by DME25, as demonstrated by ECIS (electric cell-substrate impedance sensing). YZXJ (DME25) was diluted from 1:40 to 1:125,000 (A). Dilutions below 1:25,000 showed inhibitory effect. B: 3D imaging of the adhesion determined by ECIS. Left: control HECV cells ; Right: HECV cells with DME25 at 1:1,000. X-axis: frequencies (Hz); Y-axis:Resistance; Z-axis: time in hours. C and D: cell-matrix adhesion investigated by conventional method. Namely, HECV cells were added to matrix coated culture surface. After 40 minutes, non-adherent cells were washed off. The remaining adherence cells were fixed and stained with Crystal violet. C: Images from crystal violet stained adherence cells; D: Number of adherent cell per high power field. \* p<0.01 vs control; # p<0.01 vs DME alone and FAK inhibitor alone [21].

breast, lung, colorectal and gastric cancer. In a meta-analysis of clinical studies and trials, YZXJ significantly reduced the side effects of chemotherapy, which included bone marrow suppression, leukopenia, thrombocytopenia, adverse gastrointestinal reaction and hepatotoxicity [11].

**Possible mechanism(s) underlying the anti-cancer effects by TCM**

*Effect of TCM on the immune system*

During the development and progression of cancer, adoptive and adaptive immune response can be evaded by cancer cells. Radio- and chemo- therapy can also impair the immune system, especially through bone marrow suppression. Patients receiving radio- and/or chemo-therapy may benefit from herbal medicine because it has the capacity to improve immune system functioning in numerous ways. First, TCM therapies can enhance the immune response against tumours; second, they can suppress

the immune inhibitory mechanisms and adjust the balance of the immune system; and third, they can restore an impaired immune system back to its normal state in treated patients. For example, Radix Astragali can increase INF and TNF secretion, and activate lymphocytes, natural killer (NK) cells and macrophages against tumours. It could also cooperate with IL2 to stimulate lymphokine-activated killer (LAK) cells directed against tumour cells [8, 9]. Mylabris might also restore anti-tumour T cell levels as well as TJ-41 formulation [12, 13].

*TCM induces apoptosis and cell cycle arrest of cancer cells*

TCM can induce cell cycle arrest and apoptosis of cancerous cells, thereby inhibiting tumour growth. Garlic extracts possess mainly sulphur compounds, especially allicin, diallylsulfide (DAS), diallyldisulfide (DADS), diallyltrisulfide (DATS) and ajoene, which have demonstrable anti-cancer activities. Their anti-proliferative effects have been related to the induction of apoptosis [14, 15]. Indeed, morphological changes and DNA fragmentation are seen in cells

treated with DADs and DATs [16, 17]. Bu-Zhong-Yi-Qi-Tang (BZYQT), a formula comprised of astragaloside IV, ginsenoside Rb1 and Rg1, saikosaponina and c and glycyrrhizin, seems to inhibit liver cancer cell growth by arresting the cells in G0/G1 phase [18, 19].

*TCM regulates adhesion and motility of cancer cells*

Cell adhesion and invasion are important steps in the progression to metastasis. Our institute has focussed on metastasis and angiogenesis for decades, and recently found that YZXJ is effective in inhibiting cancer cell adhesion, migration and angiogenesis in vitro and in vivo[20-22]. Although a few pathways, such as focal adhesion kinase (FAK) and Akt, seem to be involved, more research is needed in understanding how these effects are manifested.

*Anti-angiogenesis effect of TCM*

Angiogenesis is vital for cancer progression and tumour development where, without an independent blood supply, tumour size

Table 1. Sources table for YangzhengXiaoji capsule

Description	Scientific name	Part of plant
Panax ginseng	Panax ginseng C.A. Mey.	Root and rhizome
Membranaceus	Astragalusmembranaceus (Fisch.) Bge.var. mongholicus (Bge.) Hsiao	Root
Fructusligustrilucic	Ligustrumlucidum Ait.	Fruitage
Radices curcumaezedoariae	Curcuma phaeocaulis Val.	Rhizome
Ganodemalucidum	Ganodemalucidum	Cystocarp
Gynostemmapentaphylla	Gynostemmapentaphylla (Thunb) Mak	Overground
Atractylodesmacrocephala	AtractylodesmacrocephalaKoidz	Rhizome
ScutellariabarbataD.Don	ScutellariabarbataD.Don	Whole plant
Oldenlandiadiiffusa	Oldenlandiadiiffusa (willd.) Roxb.	Whole plant
Poriacocos	Poriacocos	Sderotium
DuchesneaindicaFocke	DuchesneaindicaFocke	Whole plant
SolanumlyratumThunb.	SolanumlyratumThunb.	Whole plant
Herbaartemisia	Artemisia scoparia (Bge.) Ki	Overground
CynanchumpaniculatumKitag	CynanchumpaniculatumKitag	Root and rhizome
Eupolyphagasinensis Walker	Eupolyphagasinensis Walker	Dried bodies of females
Endothelium corneumgigeriaegalli	Gallus domesticusBrisson	The wall of sand bag

would be limited due to its reliance on simple diffusion in its immediate micro-environment. The importance of this has long been realised, leading to the development and implementation of anti-angiogenic strategies in the treatment of cancer [23, 24]. The mechanisms through which these various herbal medicines exert their anti-cancerous role are now being elucidated. Together with their direct role on cancer cells, a few herbal medicines affect tumour progression through their anti-angiogenic properties. For example, Koltermann et al. [25] identified an anti-angiogenic role for the standardised extract of *G. biloba*, EGb® 761[25]. This extract enhances tyrosine phosphatases, such as SHP-1, which in turn prevents signal transduction through the Raf/MEK/ERK pathway in response to growth factor stimulation (FGF or VEGF). YZXJ can suppress angiogenesis in which FAK is involved (Figure 1) [21].

### Targeting precancerous disorders

Precancerous conditions or premalignant conditions, such as actinic keratosis, Barrett's oesophagus, atrophic gastritis and oral submucous, are generally considered

to increase significantly cancer risk. Two decades ago, researchers began examining the preventive effects of herbal formulas on different precancerous conditions. For example, Anticancer 2 tablet, composed of 6 TCM herbs, was tested on epithelial dysplasia in the cheek pouches of hamsters exposed to a carcinogen [26]. Herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin) added into the diet can be beneficial to patients with precancerous lesions in the large intestine [27]. These supplements can also suppress aberrant crypt foci in an azoxymethane-induced rat colon cancer model and induce apoptosis by regulating Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic), leading to capase-9 activation. Clinical trials using Zengshengping (ZSP) to treat oesophageal epithelial dysplasia have been carried out in 2 districts in China where there is a high risk of oesophageal carcinoma [28, 29]. YZXJ has also been reported to improve atypical dysplasia of the stomach [30]. These are a few examples of clinical studies indicating the potential therapeutic effects of TCM on precancerous conditions or lesions.

There is more evidence now showing

that herbal remedies from TCM can be developed as therapeutic approaches for management of some malignancies. The possible benefits of these remedies include: their ability to act as effective therapies for certain malignancies, reducing side effects when combined with chemotherapy/radiotherapy, and having a chemopreventive effect for certain precancerous conditions/lesions, thereby improving quality of life and prolonging survival. On the other hand, side effects and toxicity of herbal medications need to be considered and included in any evaluation made in clinical trials. Although progress in seeking clinical efficacy of TCM in cancer treatment is moving forward, well controlled and blinded clinical trials remain scarce. Investigations into the mode (s) of actions and possible clues in the active ingredient(s) in the TCM continue to be difficult tasks. However, these ancient and traditional medicines do appear to have positive effects on patients with cancer; rediscovering their values in cancer, both clinically and scientifically, will bring further value to the rising challenges of cancer treatment. ●

*“Herbal remedies from TCM can be developed as therapeutic approaches for management of some malignancies. They may well bring further value to the rising challenges of cancer treatment”*

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