

## **Synergy between TCM and Oncothermia**

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## *TCM and cancer*

Traditional Chinese medicine-based herbal medicines have gained increasing acceptance worldwide in recent years and are being pursued by pharmaceutical companies as rich resources for newer drug discovery. For many years, traditional Chinese medicines (TCM) have been applied for the treatment of cancers in China and beyond. Chinese medicine employed treatments for cancer for over two millennia. The book *The Rites of the Zhou Dynasty* (1100- 400 BCE) refers to physicians specializing in the treatment of swellings and ulcerations or necrosis and ulcerations. These terms are still utilized in the modern practice of traditional Chinese medicine to denote the study and treatment of tumors that are both benign and malignant.<sup>8</sup> Early Chinese medical texts described different types of breast tumors and discussed their clinical appearance, physiological origin and severity. Over 100 names were recorded for tumors in early medical literature. Most of these terms represent conditions that would be regarded as early cancerous conditions in the Western medical literature. The most frequently cited term for breast cancer was breast rock<sup>12</sup>. In the *Yellow Emperors Classic of Internal Medicine* (written circa 250 BCE), the first clinical picture of breast cancer was described. The prognosis was estimated to be approximately ten years after diagnosis and the process of progression, metastasis and death was detailed.

The current trend in China is to integrate, or combine Western therapies with TCM in the treatment of cancer. There are no available statistics on the proportion of women using this approach. Our collaborators in China- Hebei University TCM Department- estimate that about 70%-80% of women diagnosed with breast cancer in the metropolitan areas, where Western medicine (WM) is favoured, are using the combined approach at some point during their treatment of breast cancer while a very small fraction of women use TCM as a sole therapy. The treatments employed by the TCM physicians are aimed at controlling side effects and toxicities attributed to cancer therapies, improving quality of life, preventing recurrence and prolonging survival.

Herbal medicines are generally low in cost, plentiful, and show very little toxicity or side effects in clinical practice. However, despite the vast interest and ever-increasing demand, the absence of strong evidence-based research and the lack of standardization of the herbal products are the main obstacles toward the globalization of TCM. In recent years, TCM research has greatly accelerated with the advancement of analytical technologies and methodologies (1). Cancerous conditions are well-known in the traditional Chinese medical system. In the classics of TCM, “*Huang Di Nei Jing Di*” (黃帝內經) published more than 2000 years ago, there are descriptions of the pathogenesis, appearances and treatment principles of tumors (瘤), such as muscle, tendon and bone carcinomas; however, this term does not differentiate between malignant and nonmalignant tumors. It was not until the Sung Dynasty (ca. 1300 AD) that the first reference to cancer - the Chinese word Ai (癌) meaning malignant carcinoma - first appeared in the ancient medical book “*Wei Ji Bao Shu*” (衛濟寶書). According to the theories of TCM, cancer is caused by imbalances between endogenous physical conditions of the body and exogenous pathogenic factors. The internal condition of the body plays a dominant role in the onset of cancer. In other words, factors can induce cancer only when the body's own defense system fails. Those pathogenic factors, in Chinese medicine terms, include accumulated toxins, “heat” and blood stasis, and they attack when a person is in a weak physical condition, without the strength to resist. Furthermore, malfunction of the body-mind communication network may also trigger the development of cancer (2). So, TCM expert doctors view cancer as a systemic disease associated with the state of the whole body (or disturbance of the signaling network, to use a modern term). “Systemic” in the TCM doctors' views, means “state of the whole body”. “Cancer is the manifestation of a breakdown in the body's ability to handle pathogenic factors, not a local disease of cells or organs.” Accordingly, the treatment philosophy and strategy of TCM emphasizes holistic modulation and improvement of the whole body rather than removing the tumor mass or killing the cancerous cells. This treatment strategy is particularly enforced for cancer patients at the late stages. In these stages, the focus of treatment is extending the life expectancy and improving the quality of life of the patient; in other words, the focus is on the patient not the tumor mass (帶瘤生存). The other major principle of TCM is the emphasis on an individual therapy. For the same type of cancer in different persons, the diagnosis and treatment schemes could be very different. This is called the principle of “treatment based on symptom pattern differentiation (辨證論治)”. In other words, TCM expert doctors make the diagnosis and prepare a treatment scheme based on the assessment of the pattern of symptoms manifest in each individual. When herbs are called for, most commonly, several are used together, and the whole herbs are used, not purified compounds. Thus, in the

prescription, there will be multiple effective components delivering a comprehensive, integrated treatment of cancer through multiple targets and their associated pathways. This approach is in line with the view of TCM that cancer is a systemic disease that requires a holistic approach and medicines that can produce therapeutic actions through multiple targets. While this approach differs from that of conventional medicine, the effects of treatment still come down to biochemistry. If treatments are effective, then there must be underlying mechanisms that can be investigated and verified scientifically. Understanding these mechanisms can help us expand the efficacy of both Western and Chinese medicines in a logical, rational way.

### ***Future Prospect of TCM Herbal Medicines in Cancer Research***

The cellular and animal studies have provided strong molecular evidences for the anticancer activities of the TCM herbal medicines, tested as pure compounds or as crude extracts of the single herbs or the complex formulas. However, several important questions remain to be answered. Do TCM-derived herbal medicines possess any special effects other than those often seen with conventional drugs for cancer treatment? There has been little investigation to make a side-by-side comparison. An earlier work was conducted on the anticancer effects of protodioscine (glycosides) from the rhizome of *Dioscorea collettii* var. *hypoglauca*, a Chinese herbal remedy for the treatment of cervical carcinoma, carcinoma of urinary bladder and renal tumor for centuries, against a 60 NCI human cancer panel (3), and it was found to be specifically effective for cervical carcinoma, bladder and renal cancer cell lines. Moreover, based on an analysis of the COMPARE computer program with protodioscin as a seed compound, no other compounds in the NCI's anticancer drug screen database have a cytotoxicity pattern (mean graphs) similar to those of protodioscin, indicating that a potential novel mechanism of anti-cancer action is involved. This may be one of many methods by which the unique properties of TCM can be revealed in a concise manner. The other question to be addressed in the future is whether the methodologies and the *in vitro* and *in vivo* biological models currently employed to investigate the therapeutic nature of traditional Chinese medicines are good enough. By now 66 herbs are known that have been used for anticancer studies all over the world. They were grouped these herbal plants into seven functional groups based on the traditional usage for cancer treatment. Interestingly only a small subset of herbs is considered toxic, grouped under the category of "medicinal with cytotoxic function", the majority is not. On the other hand, the majority of TCM-derived components shown above are in the same category as the conventional anticancer drugs which induce apoptosis. In a previous study (4), we used a cell system by which the inhibitory effects of non-cytotoxic chemicals were assessed by a focus formation assay upon transfection of *ras* oncogene to the host cells. Using this system, two well-studied medicinal mushrooms *Ganoderma lucidum* and *Tricholoma lobayense* with anticancer potential were examined for their possible adverse effects on cell transformation induced by *ras* oncogene. The results indicated that both species of mushrooms strongly inhibited *ras*-induced cell transformation. However, the inhibitory effect of the mushroom extracts was not due to a direct killing of the transformed cells; rather, it seems to have been mediated through the surrounding normal cells. This normal cell-dependent growth inhibitory effect is also observed with oleanolic acid isolated from *Oldenlandia diffusa* (5). These examples suggest that, at least some, TCM medicines exert their anticancer effects through mechanism(s) other than apoptosis. Looking forward, we have to see three specific issues that will require focused more attention:

- (i) more well-designed clinical trials are required to support the effectiveness and the safety of TCM in the management of cancers/ applying together modern technology as oncothermia;
- (ii) new parameters based on the unique properties and theory of TCM are needed to assess the clinical efficacy of TCM in clinical trials; and
- (iii) new approaches to research may be needed, given the nature of TCM herbs as being fundamentally different from drugs. There is evidence that the reductionist approach, i.e., searching for one or a few active ingredients in an herb or formula, may not elucidate the efficacy of herbal medicines; a systems biology approach may be more appropriate and productive, in terms of developing effective treatment protocols.

Undoubtedly, the evaluation of the therapeutic effects and the benefits of TCM therapy for cancer patients is a significantly complex, albeit significant issue. TCM therapy, based on multiple medicinal herbs and an holistic approach to diagnosis as well as treatment, means that a clinical study of TCM treatment is more difficult and complicated than the study of single compound drugs. In addition to the conventional "standards" used for WM (western medicine) clinical trail, there is a need to develop a set of parameters

that are suitable to the assessment of TCM therapy. The effects, as well as the toxicity, of individual herbs or, especially, of single compounds derived from the herb cannot completely reflect the benefits and toxicity of the herbal combination. When whole herbs are not studied, improper or biased results and conclusions might be unavoidable (6). As a goal, to develop and involve TCM into rational cancer therapy together spin-off technology oncothermia, more well-designed intensive clinical evaluations and translational laboratory studies are absolutely needed. And, close collaboration between TCM and conventional Western medicine professions and a combination of TCM with modern multidisciplinary cutting-edge technologies like oncothermia, such as omic methodology on systems biology (7), would provide us with an attractive and effective strategy to achieve this goal for benefit patients.

### ***Anti-cancer effects and underlying mechanisms of TCM – derived complex formulas – really a “great challenge”***

There are only a few mechanistic studies on the action of TCM formulas as anticancer agents. One study was on San-Zhong-Kui-Jian-Tang (8), a complex formula comprising 17 different herbs, which is used for cancer therapy in China. It was found to induce the mitochondrial apoptotic pathway by changing Bax/Bcl-2 ratios, cytochrome c release and caspase-9 activation, but did not act on Fas/Fas ligand pathways in two human breast cancer cell lines, MCF-7 and MDA-MB-231. A similar study was carried out by the same laboratory (9) on Huang-lian-jie-du-tang (HLJDT) known to possess anti-inflammatory activity. The in vitro study conducted in two human liver cancer cell lines, HepG2 and PLC/PRF/5, found that HLJDT caused cell arrest by up-regulating the inactive form of Cdc2 and Cdc25, and down regulating the levels of Bcl-2 and Bcl-XL.<sup>1</sup> Furthermore, HLJDT increased the ratio of Bax and Bak/Bcl-2 and Bcl-XL<sup>2</sup> and the associated cell survival pathways, and subsequently triggered the mitochondrial apoptotic pathway. It was the collective actions of the herbs in the formula that were inhibiting the growth of cancer cells tested both in vitro cell lines and in vivo in nude mice. Another study is the study of a classic formula, Guizhi-fuling decoction (GZFLD) (10). The formulation consists of five herbs: Cinnamomum cassia, Paeonia lactiflora, Paeonia suffruticosa, Poria cocos, and Prunus persica. Accordingly, GZFLD inhibited the growth of HeLa cells by activating the tissue inhibitor of metallo-peptidases (TIMPs) and causing the suppression of the activity of the matrix metallo-peptidase (MMPs) that play a key role in the degradation of the extracellular matrix and promotion of cell proliferation.

<sup>1</sup> BCL2: B cell leukemia/lymphoma 2, BCL-XL: B cell leukemia/lymphoma x

<sup>2</sup> MCL-1: myeloid cell leukemia sequence, 1MDM2: murine double minute 2

In the same study, GZFLD was also shown to inhibit tumor growth and angiogenesis in an in vivo animal model. Another report (11) concerned a classic formula “bojung-bang-dock--tang (BJBDT)” consisting of Astragalus membranaceus Bunge, Atractylodes japonica Koidzumi, Coiz lacryma-jobi Linne var. ma-yuen stapf, Dioscorea batatas Decaisne, Dolichos lablab Linne, Panax ginseng C. A. Mey, Polygonatum sibiricum Delar. ex Pedouté, Poria cocos (Schw.) Wolf. Two related studies (12, 13) found that BJBDT demonstrated anti-angiogenesis by blocking VEGF/VEGFR<sup>3</sup> activities in human umbilical vein endothelial cells. Interestingly, BJBDT can prevent cisplatin-induced toxicity and apoptosis in normal MCF-10A, but not in MCF-7 and MDA MB-231 breast cancer cells, suggesting the herbal formula can be applied as a cancer chemopreventive agent (14). The synergistic effects of herbs in a TCM formula were well illustrated in a new study, in which a TCM-based formula, Realgar-indigo naturalis (RIF), was applied in the treatment of acute promyelocytic leukemia (APL). The RIF formula has three components, realgar, indigo naturalis, and Salvia miltiorrhiza of which tetra-arsenic tetrasulfide, indirubin, and tanshinone IIA, respectively, are the major active ingredients. The study demonstrated that tetraarsenic tetrasulfide is the principle component of the formula, while tanshinone IIA and indirubin are the adjuvant ingredients. Together these herbs have shown a synergistic action against APL effective in both in vitro and human clinical studies.

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<sup>3</sup> VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor