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Overview

Chinese Medicine in Cancer Treatment – How is it Practised in the East and the West?

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Abstract

Chinese medicine therapies in cancer treatment are very common in the East. Although it is usually classified as a form of complementary and alternative therapy in the West, Chinese medicine is an independent medical profession in Hong Kong and mainland China. It has a different perspective in understanding health and diseases compared with Western medicine. In oncology practice, whereas Western medicine focuses on direct tumour eradication by surgery, radiation therapy and systemic therapies, Chinese medicine focuses on restoring body balance and enhancing the body's defences (immunity), in addition to some cytotoxic herbal therapies. Most often patients, especially those in the East, receive both treatments. Chinese medicine is also commonly used to reduce side-effects from chemotherapy or radiation therapy, to aid recovery after an operation, to palliate symptoms and to address survivorship issues. However, this raises concerns of drug–herb interactions and toxicity in combination therapies. Commonly used Chinese medicine treatment modalities include acupuncture, moxibustion, diet therapy, prescribed Chinese medicine herbal decoction, single Chinese medicine herbs or supplements and tai chi. Although there is an increasing trend of Chinese medicine use in cancer patients in both the East and the West, the scientific evidence of safety and efficacy is often questioned by oncologists. This article reviews the current evidence in different Chinese medicine therapies in cancer management in both the East and the West.

Key words: Cancer management; Chinese medicine; herbal medicine; traditional Chinese medicine

Statement of Search Strategies Used and Sources of Information

A PubMed search was conducted on 20 February 2019 using the search terms: (Cancer OR Oncology) AND (Traditional Chinese Medicine OR Acupuncture OR Chinese Medicine). Filters applied included (Clinical Trial), (Review), (Full text), (English) and (Humans). In total, 172 papers were found, and relevant articles were selected. In addition, the professional knowledge of Chinese medicine of the authors was also applied.

Introduction

Chinese medicine or traditional Chinese medicine has a history of more than 2000 years and is widely practised in Hong Kong, China and other Chinese societies. Although Chinese medicine is usually classified as a form of complementary and alternative therapy in the West, Chinese medicine is an independent medical profession in Hong Kong and mainland China. For instance, in Hong Kong, a former British colony with medical education greatly resembling that of Great Britain, registered Chinese medicine practitioners are independently regulated by the Chinese Medicine Council [1]. All Chinese medicine practitioners must have undertaken at least 5 years of professional undergraduate study before they can sit the Chinese medicine licensing examination. They are also entitled to have the same legal rights as medical doctors,

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such as issuing certificates of sick leave, certifying a person's pregnancy and completing disability certification forms [2]. Thus, with these dual and parallel systems of medicine in place, it is very common for Chinese cancer patients to seek medical care from both Chinese and Western medicine.

Western medicine oncologists often doubt the effectiveness and safety of Chinese medicine for cancer patients. The other extreme scenario is that some patients may only opt for alternative medicine instead of conventional therapies, including surgery, radiation therapy and systemic treatment. Park *et al.* [3] reported on 840 patients with four commonly seen solid malignancies (lung, prostate, breast and colorectal cancers). There was an increased risk of death, with a hazard ratio of 2.5 (95% confidence limits 1.88–3.27), if patients only sought alternative medicine treatment alone without conventional therapies. Another recent large retrospective study of the National Cancer Database of more than 1.9 million patients with these four cancer types showed a similar result [4]. Johnson *et al.* [4] found that the use of complementary medicine was associated with a refusal of conventional cancer treatment and with a two-fold greater risk of death compared with patients who received conventional cancer therapy. The results from these two studies have raised concerns and controversy among the use of Chinese medicine in cancer patients. There are reasonable doubts that the results from these two studies may not be generalised to Chinese medicine. In the former study, 'alternative medicine' was defined as sole unproven therapy without conventional cancer therapies. By contrast, Chinese medicine therapies are usually used to complement conventional therapies. In the latter study 'complementary medicine' was defined as 'Other - unproven: cancer treatments administered by nonmedical personnel'. It is doubtful whether this could be applied to Chinese medicine as Chinese medicine is often administered by trained Chinese medicine practitioners. All in all, Chinese medicine in Chinese societies is considered a mainstream medicine instead of 'alternative medicine'.

According to a survey of cancer patients in Hong Kong conducted in 2009 [5], 57% of cancer patients used at least one form of Chinese medicine therapy. Among those who were on chemotherapy, 60% also concurrently received Chinese herbal medicine therapy. On the other hand, almost two-thirds of all patients did not inform their physicians about Chinese medicine use. This can cause issues of unidentified drug–herb interactions.

Although the popularity of using Chinese medicine among cancer patients is undeniable, there are often reservations among Western oncologists about the lack of high-quality evidence to support its use. This can be attributed to a number of reasons. First, there is a general lack of understanding of Chinese medicine by Western medicine practitioners. For example, on the Cancer Research UK website [6], feng shui is listed under traditional Chinese medicine. Feng shui, while widely practised in the Chinese community, is traditionally practised to 'harmonise the environment to promote good health and wealth of the host'. It has little association with Chinese medicine. Second, although there have been numerous clinical studies of Chinese medicine in cancer treatment conducted in mainland China over the past decades, most of them have been published in Chinese-language journals and many are of an inadequate standard from a Western medicine methodology perspective. Third, there is a lack of standardisation of Chinese medicine practise and government regulation of Chinese medicine practitioners in the West, except in Australia [7] and the Canadian provinces of Ontario and British Columbia [8,9]. Western medical doctors even sometimes question the qualifications and creditability of Chinese medicine practitioners in their own countries.

On the bright side, medical evidence for various modalities of Chinese medicine for cancer treatment has been building for the past 20 years. This article reviews the recent evidence of the most commonly used Chinese medicine therapies in cancer patients, including acupuncture, herbal medicine decoction, herbal products or supplements. Tai chi, diet therapy and massage therapy are excluded as they are not commonly used to treat cancer. Issues of drug–herb interactions and placebo control will also be addressed.

Perspectives of Chinese Medicine

Although it is outside the scope of this article to discuss the complex theories and schools of thought of Chinese medicine, it will be beneficial to have a simple understanding of Chinese medicine, especially in relation to cancer treatment.

Chinese medicine is a complete independent medical system and mechanism, in contrast to Western medicine. Chinese medicine has its unique philosophies and theories. Chinese medicine treats the body as a whole and sees any disease as a result of disturbance of the balance of yin and yang and the Five Organs System (Five Element Theory). In the diagnosis of disease, Chinese medicine has its own disease classifications and diagnostic criteria [10]. This is why Western physicians find Chinese medicine confusing, as separate diseases in Western medicine may be grouped as the same disease in Chinese medicine and sometimes the reverse is the case.

Chinese medicine sees cancer as the result of a disturbance of the body's harmony. According to the classic Chinese medicine book *The Yellow Emperor's Inner Canon*, cancer is caused by exopathogens, environmental factors, emotional maladjustment and improper diet [11]. These pathogenic factors disturb the Five Organs System; cause stagnation of 'qi', blood and body fluids; and cause an accumulation of 'toxins'.

Treatment therefore aims to counterbalance these factors, by strengthening the host immunity, detoxifying, restoring the flow of qi and blood, and softening hard tumours. Now, Chinese medicine is usually used in conjunction with Western medicine and the aim of Chinese medicine treatment varies with different stages of cancer and concurrent Western medicine therapies. The role of Chinese medicine in different stages is summarised in Figure 1.

The evidence of each treatment modality is further elaborated below.

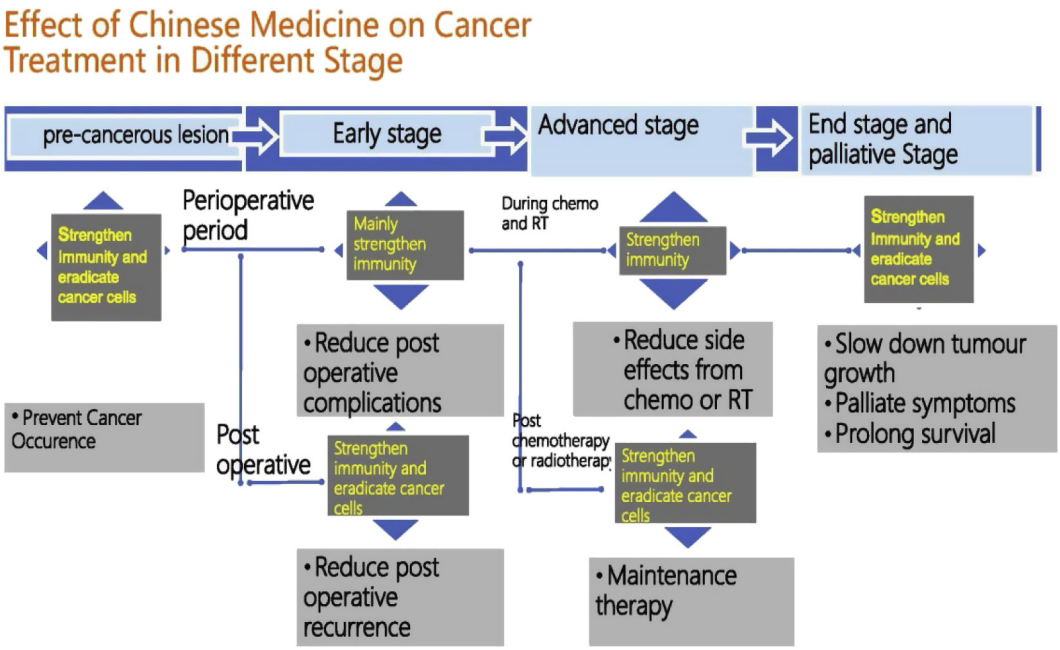

Fig 1. Effect of Chinese medicine on cancer treatment in different stages. Adapted and amended from Clinical Practice Guidelines of Chinese Medicine in Oncology, China Association of Chinese Medicine.

Acupuncture

Among all Chinese medicine treatment modalities, acupuncture has the greatest amount of evidence to support its clinical use in cancer management. Acupuncture involves the insertion of fine needles into the designated skin acupoints to stimulate muscles, fascia and nerve fibres, to achieve neuro-hormonal changes in the body. In Chinese medicine, acupuncture helps to restore the flow of qi (energy) in meridians (energy channels) to achieve therapeutic effects.

In oncology, acupuncture is mainly used in a supportive role in cancer treatment. The National Comprehensive Cancer Network (NCCN) [12–16] guidelines recommend acupuncture for a number of conditions, including acute cancer pain, nausea and vomiting in the palliative setting, cancer-related fatigue, chemotherapy-related nausea and vomiting, as well as various survivorship issues, such as vasomotor symptoms. Perhaps acupuncture is most well-known for its analgesic effect. Acupuncture can enhance endogenous endorphins and has been shown to be effective in both non-cancer pain [17,18] and cancer pain [17]. Chiu *et al.* [19] conducted a meta-analysis of the effect of acupuncture on cancer pain in all published randomised controlled trials (RCT) in both Chinese and English literature. They included 29 RCTs, yielding 36 effect sizes. The overall effect on cancer-related pain was −0.45 (95% confidence interval −0.63 to −0.26). In a subgroup analysis, malignancy-related and surgery-induced pain were found to be the most effectively treated with acupuncture (effect size −0.71 and −0.40; 95% confidence interval −0.94 to −0.48 and −0.69 to −0.10). Despite these positive results, we suggest that acupuncture should usually be used in conjunction with pharmacological intervention including both opioid and non-opioid analgesics. This is consistent with NCCN guidelines [12].

Acupuncture is commonly used to relieve chemotherapy-induced peripheral neuropathy (CIPN) [20]. A systematic review of 48 RCTs suggested that no single agent can be recommended for the prevention of CIPN [21]. Only duloxetine receives a 'moderate recommendation' for CIPN treatment and there is only weak evidence that other agents, such as gabapentin, are efficacious in the treatment of the neuropathic pain caused by CIPN. However, there have been multiple case series showing beneficial effects of acupuncture in helping CIPN [22]. Franconi *et al.* [20] published a systematic review of acupuncture studies on CIPN in 2013. They identified seven high-quality studies, all of which showed acupuncture to have a positive effect on CIPN. Although there was a high degree of heterogeneity among the study designs, the number of subjects recruited and the outcome measures, the review provides a foundation of clinical evidence for further more robust studies. The results of this systematic review are summarised in Table 1.

Acupuncture has also been found to be effective in reducing chemotherapy-induced neutropenia and breast cancer-related lymphoedema. In 2015, a review paper found that acupuncture may be able to reverse myelosuppression from chemotherapy, although the article also found problems in the research methods of the studies included [23].

The evidence of acupuncture for various oncological conditions is listed in Table 2.

Herbal Medicine Decoction

Although acupuncture is more common than herbal decoction in the West, the reverse is true in Chinese

Table 1
Evidence of acupuncture in chemotherapy-induced peripheral neuropathy. Adapted from Franconi *et al.* [20]

Study	Year	Number of patients	Follow-up	Study design	Intervention	Outcomes	Results
Alimi *et al.*	2003	90	2 months	Prospective randomised controlled trial	Auricular acupuncture versus placebo acupuncture and seeds	VAS pain score and medication consumption	True acupuncture better than placebo
Wong and Sagar	2006	5	16 weeks (two 6-week courses with a 4-week therapy-free interval)	Prospective case series	Acupuncture (no control)	Pain score and WHO CIPN grade	Improvement
Xu *et al.*	2010	64	Not known	Randomised controlled trial	Acupuncture versus cobamamide	Questionnaire of peripheral neuropathy	Acupuncture better than cobamamide
Bao *et al.*	2011	1	22 weeks	Case report	Acupuncture (no control)	VAS pain score	No more symptoms
Donald *et al.*	2011	18	6 weeks	Retrospective case series	Acupuncture (no control)	Subjective symptoms	82% improved
Schroeder *et al.*	2012	11	10 weeks	Retrospective controlled non-randomised trial	Acupuncture and best medical care versus best medical care	Nerve conduction studies	Acupuncture better than control
Tian *et al.*	2011	76	Not known	Randomised controlled trial	Warm acupuncture and moxibustion versus neurotropin	Quality of life and neurotoxic symptoms	Acupuncture better than neurotropin

CIPN, chemotherapy-induced peripheral neuropathy; VAS, visual analogue scale; WHO, World Health Organization.

societies. Most herbal medicine treatment is given in herbal formulae (decoction) consisting of multiple herbs. The combination use of herbs is believed to enhance the therapeutic action, reduce side-effects and treat multiple 'targets' to restore the body's balance. Although the herbal formula is highly personalised, there are hundreds to thousands of template formulae from 2000 years of Chinese medicine books to choose from. Most often Chinese medicine practitioners choose one or more template formula and then add or take away constitute herbs according to the individual patient's body status. The prescription therefore usually changes with treatment stage and body need according to Chinese medicine principles. This contrasts with Western oncology, in which different patients with the same type of malignancy usually receive the same drug or regimen according to the latest scientific evidence.

Wong *et al.* [40] reported a case series of 189 locally advanced or metastatic pancreatic cancer patients treated by Chen (one of the authors of this article) with Chinese herbal medicine. The median overall survival reported was 15.2 months, higher than that of 11.1 months when treated with FOLFIRINOX chemotherapy [41]. Two patients with metastatic diseases treated with Chinese medicine alone lived more than 8 years. However, the patient group was rather heterogenous in terms of histology (with four neuroendocrine tumours and one sarcoma) and concurrent Western oncology treatment, ranging from chemotherapy to palliative care alone. This reflects the real-world scenario in which Chinese medicine is practised in a very heterogeneous group of patients. This also makes it very difficult to conduct the more commonly accepted RCTs to assess the efficacy of Chinese medicine.

In addition, Chen *et al.* [42] reported more than 1000 cases series treated with herbal medicine decoction and which resulted in many favourable outcomes. However, those are real-world data that have not been formally analysed with modern research methods. Wong's group has been carrying out a further survival analysis of these records. Chen *et al.* [42] also suggested changing cytotoxic herbs regularly to minimise potential accumulated toxicities and to reduce herb resistance by cancer cells. This is very similar to the concept of re-challenging anti-epidermal growth factor receptor therapy in metastatic colon cancer, as clonal selection changes throughout treatment, as measured by circulating tumour DNA [43].

Good-quality English-language published trials in this area are rare. Liu *et al.* [44] reported a RCT of 474 stage III–IV non-small cell lung cancer (NSCLC) patients and compared the outcome of additional Chinese herbal medicine (IM group) with the standard therapy (radiotherapy, chemotherapy and optimal supportive therapy according to NCCN guidelines) to standard therapy alone (WM group). The median overall survival was 16.60 and 13.13 months in the IM and WM groups, respectively ($P < 0.01$). Moreover, nausea and vomiting were less frequently reported in the IM group ($P < 0.05$) Another group in China reported the use of maintenance Chinese medicine instead of chemotherapy in advanced NSCLC patients [45]. Sixty-four patients with an initial response to chemotherapy were randomised 1:1 to the traditional Chinese medicine arm

Table 2
Selected publications on the use of acupuncture for various oncological conditions except chemotherapy-induced peripheral neuropathy

Study	Year	Patient group	Number of patients	Study design	Methods	Intervention	Results and remark
Fatigue (chemotherapy- or radiotherapy-induced)							
Mao *et al.* [24]	2014	Breast cancer survivors on aromatase inhibitor	67	Randomised controlled trial	3 groups - real acupuncture - sham acupuncture - wait-list control	EA For 12 weeks	Produced significant improvement in fatigue ($P = 0.0095$), anxiety ($P = 0.044$) and depression ($P = 0.015$)
Mao *et al.* [25]	2009	Cancer patients undergoing radiotherapy	16	Single-arm trial	N/A	Acupuncture for 12 weeks	Average fatigue and energy level remained stable during and after radiotherapy. 8 (50%) and 6 (37%) perceived their fatigue as stable and better at the end of radiotherapy
Molassiotis *et al.* [26]	2012	Breast cancer patients	246	Randomised controlled trial	N/A	Acupuncture for 6 weeks	2 groups - acupuncture plus usual care - usual care Significantly improved physical fatigue and mental fatigue (both $P < 0.001$), anxiety and depression (both $P < 0.001$) and quality of life (physical, functional, emotional and social functioning well-being) (all $P < 0.05$)
Vickers *et al.* [27]	2004	Cancer patients who completed cytotoxic chemotherapy	37	Phase II trial	N/A	Acupuncture for 4 or 6 weeks	Mean improvement in fatigue following acupuncture was 31.1% (95% CI 20.6 −41.5%)
Joint pain (chemotherapy-induced)							
Hershman *et al.* [28]	2018	Postmenopausal women with early-stage breast cancer on aromatase inhibitor	226	Randomised controlled trial	3 groups - true acupuncture - sham acupuncture - wait-list control	Acupuncture for 12 weeks	Produced statistically significant reduction in joint pain at 6 weeks ($P = 0.01$)
Crew *et al.* [29]	2010	Postmenopausal women with early-stage breast cancer on aromatase inhibitor	43	Randomised controlled trial	2 groups - true acupuncture - sham acupuncture	Acupuncture for 6 weeks	Produced significant improvement in joint pain and stiffness. Had lower mean BPI-SF worst pain score ($P < 0.001$), pain severity ($P < 0.003$) and pain-related interference ($P = 0.002$)

Table 2 (*continued*)

Study	Year	Patient group	Number of patients	Study design	Methods	Intervention	Results and remark
Insomnia							
Frisk *et al.* [30]	2012	Breast cancer survivors	45	Randomised controlled trial	2 groups - EA - hormone therapy	EA for 12 weeks	WHQ ($P < 0.001$) and PGWB ($P = 0.002$) improved. All sleep parameters improved ($P < 0.05$) and HFS decreased by 80%
Xerostomia							
Johnstone *et al.* [31]	2001	Head and neck cancer patients who received radiotherapy	18	Single-arm trial	N/A	Acupuncture for 3–4 weeks	Acupuncture contributed to relief from xerostomia to varying degrees
Cancer pain							
Chiu *et al.* [19]	2017	Patients of various cancer types	2213	Systematic review and meta-analysis	N/A	Acupuncture	Acupuncture significantly reduced cancer-related pain ($P < 0.001$)
Alimi *et al.* [32]	2003	Patients of various cancer types	90	Randomised controlled trial	3 groups - auricular acupuncture at points with detectable electrodermal signal - auricular acupuncture at points without detectable electrodermal signal (placebo points) - auricular seeds fixed at placebo points	Acupuncture for 2 months	Pain intensity decreased ($P < 0.001$)
Chemotherapy-induced nausea and vomiting							
Ezzo *et al.* [33]	2005	Patients of various cancer types	1247	Systematic review and meta-analysis	N/A	Acupuncture	Acupuncture reduced the proportion of acute vomiting ($P < 0.04$)
Reindl *et al.* [34]	2006	Children with solid tumours receiving chemotherapy	11	Randomised controlled trial	2 groups - chemotherapy with anti-emetic medication plus acupuncture - chemotherapy with anti-emetic medication alone	Acupuncture given on day 1 of chemotherapy and consecutive days of the chemotherapy course	Acupuncture enabled patients to experience higher levels of alertness during chemotherapy and reduced nausea and vomiting (not significant).
Vasomotor symptoms (hot flushes)							
Mao *et al.* [35]	2015	Breast cancer survivors	120	Randomised controlled trial	4 groups - real acupuncture - sham acupuncture - gabapentin - placebo pills	EA for 8 weeks	Mean reduction in HFCS was greatest in EA group ($P < 0.001$)
Walker *et al.* [36]	2010	Breast cancer patients on hormone therapy with tamoxifen or arimidex	50	Randomised controlled trial	2 groups - acupuncture - venlafaxine	Acupuncture for 12 weeks	Both groups exhibited significant decreases in hot flashes, depressive symptoms and other quality-of-life symptoms, including significant improvements in mental health

(*continued on next page*)

Table 2 (*continued*)

Study	Year	Patient group	Number of patients	Study design	Methods	Intervention	Results and remark
Deng *et al.* [37]	2007	Breast cancer patients	72	Randomised controlled trial	2 groups - real acupuncture - sham acupuncture	Acupuncture for 4 weeks	Real acupuncture was associated with 0.8 fewer hot flashes per day than sham at 6 weeks (95% CI −0.7 to 2.4; $P = 0.3$)
Neutropenia							
Lu *et al.* [38]	2009	Ovarian cancer patients with chemotherapy	21	Randomised controlled trial	2 groups - real acupuncture - sham acupuncture	Acupuncture for 6 weeks	The incidence of grade 2–4 leukopenia was less in the acupuncture arm than in the sham arm ($P = 0.02$)
Lymphoedema							
Bao *et al.* [39]	2018	Breast cancer survivors with BCRL	82	Randomised controlled trial	2 groups - acupuncture - wait-list control	Acupuncture for 6 weeks	It did not significantly reduce BCRL in pre-treated patients receiving concurrent lymphoedema treatment

BCRL, breast cancer-related lymph; BFI-SF, Brief Pain Inventory-Short Form; CI, confidence interval; EA, electroacupuncture; HFCS, Hot Flash Composite Score; HFS, Hot Flush Score; PGWB, Psychological and General Well-being Index; WHQ, Women's Health Questionnaire.

(treated with herbal injection [Cinobufacini, 20 ml/day, days 1–10], herbal decoction [days 1–21] and Chinese acupoint application [days 1–21], $n = 32$) or to the chemotherapy arm (treated with pemetrexed [non-squamous NSCLC, 500 mg/m^2 on day 1], docetaxel [75 mg/m^2 on day 1] or gemcitabine [1250 mg/m^2, days 1 and 8], $n = 32$). The 1-year survival rate of traditional Chinese medicine treatment was found to be higher than that of chemotherapy (78.1% versus 53.1%, $P = 0.035$). However, there was no difference between two groups in time to tumour progression (TTP) and overall survival ($p = 0.114$ and $P = 0.601$, respectively). Chinese medicine herbal formulae were also shown to be effective in supportive treatment. In total, 406 patients on opioid analgesic were randomised into the Chinese medicine group, which were treated according to Chinese medicine syndromal differentiation, with the control group receiving phenolphthalein tablets only [46]. Patients in the Chinese medicine group were found to have much less constipation than those in the control group, as measured by the Cleveland constipation score ($P < 0.05$). The total analgesic efficiency of the Chinese medicine group was also better than the control group (93.5% versus 86.4%, $P < 0.05$).

Meta-analyses reviewing both Chinese- and non-Chinese-language literature may give better estimates of the benefit of Chinese medicine. A meta-analysis published in the *Journal of Clinical Oncology* in 2006 [47] showed that Astragalus-based Chinese medicine improved the outcomes of lung cancer patients on platinum-based chemotherapy. In this meta-analysis, 34 randomised studies representing 2815 patients were included. Twelve studies ($n = 940$ patients) reported a reduced risk of death at 12 months (risk ratio = 0.67; 95% confidence interval 0.52–0.87). Thirty studies ($n = 2472$) reported improved tumour response data (risk ratio = 1.34; 95% confidence interval 1.24–1.46). A better result was seen in a subgroup analysis: in two studies ($n = 221$ patients), Jin Fu Kang (a type of Astragalus-based Chinese medicine product) reduced the risk of death at 24 months (risk ratio = 0.58; 95% confidence interval 0.49–0.68). Astragalus was suggested to work by stimulating macrophage and natural killer cell activity and inhibiting T-helper cell type 2 cytokines. Another meta-analysis, which included 2079 patients, showed the effect of Chinese medicine herbs on hepatocellular carcinoma patients [48]. Chinese medicine combined with chemotherapy, compared with chemotherapy alone, improved survival at 12, 24 and 36 months (relative risk 1.55, 95% confidence interval 1.39–1.72, $P < 0.000$; relative risk 2.15, 95% confidence interval 1.75–2.64, $P < 0.000$; relative risk 2.76, 95% confidence interval 1.95–3.91, $P < 0.000$). However, both meta-analyses addressed the issue of the low quality of many published trials and robust trials are needed to confirm these findings. One systemic review [49] was carried out to determine whether a decoction containing huangqi compounds helped to reduce side-effects from chemotherapy in colorectal cancer patients. The authors did not find any benefit of the Chinese medicine compound due to the low quality of the trials published.

Herbal Products

Single herbs or herbal products are commonly used by Chinese patients in cancer management. Frequently their use is not under the supervision of Chinese medicine practitioners but rather as a Chinese medicine form of 'vitamins' for the general public. For instance, peanut skin,

either boiled into a decoction or as readily available extract powder, is commonly used by Hong Kong patients to prevent thrombocytopenia due to the myelosuppressive effect of chemotherapy agents such as gemcitabine. Peanut skin is a form of 'haemostatic' herb in Chinese medicine. Although clinical trials are lacking, there is a pre-clinical study supporting its use. One Japanese group [50] recently found that peanut skin extract accelerated proplatelet formation from megakaryocytes in a liquid cell culture system of CD34 human cells.

Two other common 'anti-cancer' herbs in Chinese societies are *Ganoderma lucidum* (Ling Zhi) and *Cordyceps sinensis*. *Ganoderma lucidum* is a mushroom used as a cancer chemotherapy agent in ancient China. It has been shown to inhibit constitutively active transcription factors nuclear factor kappa B and AP-1, and suppress cell adhesion and cell migration of invasive breast and prostate cancer cells [51]. *Cordyceps sinensis* is a fungus that parasitises on the larva of *Lepidoptera* and is very valued in Chinese medicine. There is laboratory evidence that it has anti-metastatic action by suppressing the invasiveness of cancer cells via inhibiting the activity of matrix metalloproteinase (MMP)-2 and MMP-9, and accelerating the secretion of tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 from cancer cells [52]. It also has immunity-modulating and apoptosis-inducing effects [53]. However, a recent study showed that *Cordyceps sinensis* decreases radiosensitivity [54] and promotes the growth of prostate cancer cells [55] by increasing the production of testosterone and stimulating the AR-dependent pathway. Clinical studies are therefore required before these herbs can be recommended.

Another herbal product worth discussing is PHY906 (KD018). It is a four-herb Chinese medicine formula based on a 1800-year-old classical Chinese medicine formula 'huang qin tang'. It has been developed as a drug by a Yale group. It has been shown to augment the effect of sorafenib and nivolumab against hepatocellular carcinoma [56,57]. In a phase II study of combining capecitabine with PHY906 in 25 pancreatic cancer patients [58] as salvage chemotherapy after failing gemcitabine, the median progression-free survival was 10.1 weeks (range 0.4–54.1) and the median overall survival was 21.6 weeks (range 0.4–84.1). PHY906 is also found to relieve diarrhoea and the hand-foot syndrome side-effect of capecitabine treatment [59]. Another trial of using PHY906 with capecitabine in neoadjuvant chemoradiation of rectal tumour is underway to determine if gastrointestinal side-effects can be reduced (NCT02178644) [60].

Drug–Herb Interactions and Toxicity

There have been many anecdotal reports of liver toxicity with traditional Chinese herbal medicine. A recent literature review [61] found 77 published cases or case series of hepatotoxicity possibly associated with 57 different herbs and herbal mixtures. Causality was likely or probable in only around a half (28 of 57 herbal products) of them. Commonly used Chinese herbs, such as huang qin (*Scutellaria baicalensis*) and ho shou wu have also been reported. These reports need to be studied with caution, as hepatotoxicity can also be caused by contaminants in the herbs, other medications or underlying diseases. Another point of note is the high prevalence of chronic hepatitis B infection in Asia (7.8% in Hong Kong [62]). It is well known that hepatitis B reactivation is more common in patients receiving chemotherapy. The effect of hepatitis B reactivation with concurrent use of Western drugs and Chinese herbs in these patients warrants further study.

A recent report [63] showed that the leading class of implicated drugs in drug-induced hepatotoxicity in hospitalised patients in China was traditional Chinese medicines or herbal and dietary supplements (26.81%). However, the study did not distinguish between prescribed Chinese medicine herbs by a Chinese medicine practitioner and over-the-counter herbal products. Also, the risk of severe liver toxicities remained low in the study. This study highlighted that Chinese medicine is not completely non-toxic, as many Chinese patients have assumed.

Our group is building a database of the incidence and causes of liver and renal toxicity in combined use of systemic oncology therapies (chemotherapy, targeted therapy or immunotherapy) with herbal medicine. Our preliminary (unpublished) result found that in 254 solid tumour patients with normal baseline liver function in our clinic, 25% received concurrent Chinese medicine herbal treatment in addition to conventional systemic therapy. Only two patients in Chinese medicine group and four in the control group developed grade 2 or above liver function derangement (raised serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) or bilirubin). However, there was no difference in incidence between these two group ($P = 0.571$). The final result, when available, will be useful to ensure the safety of the combination use of Western and Chinese oncology treatment.

Drug–herb interactions have also been under the spotlight, as many oncological drugs, such as tamoxifen and abiraterone, require the cytochrome system for activation or metabolism. The Western herb St John's Wort [64] is well known for its cytochrome inhibition. It is reasonable to assume that herb–drug interactions do exist for Chinese medicine herbs, especially when multiple herbs are commonly used in a decoction, as discussed above. Therefore, potential pharmacokinetic and pharmacodynamic interactions is one of the reasons why oncologists often advise their patients against Chinese medicine herbs use. The Hospital Authority in Hong Kong (a statutory health organisation similar to the National Health Services in the UK) maintains a drug–herb interaction database by reviewing published evidence to alert medical practitioners of potential drug–herb interactions [65]. However, given the lack of high-quality studies published, the database is far from perfect. Nevertheless, this database serves as a framework for further research.

Issues with Placebo Controls

A lack of high-quality placebo controls is a common problem in Chinese medicine studies. For acupuncture, the

use of unsuitable placebo controls can lead to serious misinterpretation of acupuncture trials [66]. Sham acupuncture by needling in irrelevant sites, away from classical point locations, which was once widely used as the placebo in pain trials, was also found to have an analgesic effect of 50%, in comparison with 70% for real acupuncture [67]. In view of this problem, the Hong Kong group led by Lao (the last author of this article) has published a guideline to address the research methodology and particularly on choosing an adequate control in an acupuncture trial [68]. Several placebo controls have been suggested. First, the waitlist control/non-intervention control is the simplest one, but it is only recommended in the early stages (stage I/phase I) of a study, as it is not possible to differentiate between the placebo effect and the therapeutic effect and this control tends to over-estimate the true effect of acupuncture. Second, a non-insertion sham control uses a special sham needle that resembles real needling but without penetrating the skin. This method is good to control for the placebo effect for acupuncture, but the blinding effect may not last long as subjects might learn the real acupuncture experience by visiting other acupuncturists. Thus, this method is recommended for short-term clinical trials enrolling patients with little acupuncture experience. Third, the needle-insertion sham acupuncture control provides needling to irrelevant points, as mentioned above. It resembles real acupuncture well but probably produces non-specific physiological effects of needling and diminishes the true effect of acupuncture. A pilot study to validate sham needling is suggested prior to a formal trial. Finally, combined controls with non-insertion and needle-insertion sham acupuncture can enhance blinding in both groups, but it can be difficult to implement in practise.

On the other hand, there is a lack of studies on how to address the placebo issue for herbal trials. The majority of Chinese medicine herbal trials are not controlled. For those RCTs reported, most are of poor quality in methodology, including placebo preparation. In a Chinese-language review published in 2008 to evaluate the validity of placebo in all herbal trials (not limited to oncology), only 77 placebo blinded clinical trials were identified [69]. Only two articles validated the comparability between the testing drug and placebo. It is also difficult to provide a good placebo in trials using a herbal decoction, given the distinct colour and taste of herbal decoctions. A recent study suggested that a satisfactory placebo capsule can be made for herbal trials [70]. Another way to solve this problem is to conduct the herbal trial using granules (with excipients) with active herbal ingredients and to make the placebo in granules with the same excipients but without active compounds. The latter method is currently being used in a non-oncology study conducted by our institution [71].

Future Perspectives and Conclusion

Except for acupuncture, the current evidence on the use of Chinese medicine in oncology treatment is not strong. One must note that Chinese medicine has a long history and heritage, and its own way of documenting cases and passing on knowledge. It is only recently that Chinese medicine has been put under the scrutiny of evidence-based medicine.

Given the fundamental difference between Chinese and Western medicine approaches in treating disease, RCTs according to a diagnosis based on Western medicine may not be optimal and appropriate to assess the efficacy of Chinese medicine. There is also a practical difficulty in conducting pharmaceutical clinical trials, as Chinese medicine does not use the Western 'one-size-fits-all' approach, but rather Chinese medicine herbal formulae are often highly personalised to cater for individual needs. Therefore, using a pragmatic trial design may suit Chinese medicine more [72]. Interestingly, Chinese medicine philosophy apparently matches with the current concept of precision oncology.

Hong Kong will have its first Chinese Medicine Hospital in operation in 2024 [73]. It is envisioned to be a base for conducting high-quality research and bridging Chinese medicine with Western modern medicine. For instance, the pilot programme group of the Chinese Medicine Hospital has recently published a guideline for using Chinese medicine in cancer palliative care [74]. Other preparatory work for this hospital is still ongoing. Our group and many more collaborating institutions in mainland China and the USA are actively pursuing clinical research in Chinese medicine and hope to produce more evidence for Chinese medicine use for our future cancer patients.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.05.016.

References

[1] *Composition, Functions and Member List of the Chinese Medicine Council of Hong Kong, Hong Kong* 2019. https://www.cmchk.org.hk/pcm/eng/#../../eng/main_intro01.htm.

[2] *Certification for employee benefits (Chinese medicine) (miscellaneous amendments) ordinance 2006 commonly asked questions Hong Kong* 2006. https://www.labour.gov.hk/eng/public/wcp/ChineseMedicineFAQ.pdf.

[3] Park HS, Johnson SB, Yu JB, Gross CP. Use of alternative medicine for cancer and its impact on survival. *JNCI* 2017;110:121–124.

[4] Johnson SB, Park HS, Gross CP, Yu JB. Complementary medicine, refusal of conventional cancer therapy, and survival among patients with curable cancers. *JAMA Oncol* 2018;4:1375–1381.

[5] Lam YC, Cheng CW, Peng H, Law CK, Huang X, Bian Z. Cancer patients' attitudes towards Chinese medicine: a Hong Kong survey. *Chin Med* 2009;4:25.

[6] *Traditional Chinese Medicine*. UK: Cancer Research UK; 2018, https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/complementary-alternative-therapies/individual-therapies/traditional-chinese-medicine.

[7] *Chinese Medicine Board of Australia- registration. Australia* 2019. https://www.chinesemedicineboard.gov.au/Registration.aspx.
[8] *The College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario (CTCMPAO) Canada* 2019. http://www.ctcmpao.on.ca/.
[9] *The College of Traditional Chinese Medicine Practitioners and Acupuncturists of British Columbia. Canada* 2019. https://www.ctcma.bc.ca/.
[10] Lu AP, Jia HW, Xiao C, Lu QP. Theory of traditional Chinese medicine and therapeutic method of diseases. *World J Gastroenterol* 2004;10:1854–1856.
[11] Liu J, Wang S, Zhang Y, Fan HT, Lin HS. Traditional Chinese medicine and cancer: history, present situation, and development. *Thorac Cancer* 2015;6:561–569.
[12] Adult Cancer Pain. *NCCN clinical practice guidelines in oncology*, 1st ed. 2019. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
[13] Antiemesis. *NCCN clinical practice guidelines in oncology*, 1st ed. 2019. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
[14] Cancer-related Fatigue. *NCCN clinical practice guidelines in oncology*, 1st ed. 2019. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
[15] Palliative Care. *NCCN clinical practice guidelines in oncology*, 1st ed. 2019. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
[16] Survivorship. *NCCN clinical practice guidelines in oncology*, 1st ed. 2019. https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.
[17] Lu W, Rosenthal DS. Acupuncture for cancer pain and related symptoms. *Curr Pain Headache Rep* 2013;17:321.
[18] Patil S, Sen S, Bral M, Reddy S, Bradley KK, Cornett EM, *et al*. The role of acupuncture in pain management. *Curr Pain Headache Rep* 2016;20:22.
[19] Chiu HY, Hsieh YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. *Eur J Cancer Care* 2017;26:e12457.
[20] Franconi G, Manni L, Schröder S, Marchetti P, Robinson N. A systematic review of experimental and clinical acupuncture in chemotherapy-induced peripheral neuropathy. *Evid Based Complement Alternat Med* 2013, https://doi.org/10.1155/2013/516916; 2013.
[21] Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, *et al*. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014;32:1941–1967.
[22] Wong R, Sagar S. Acupuncture treatment for chemotherapy-induced peripheral neuropathy – a case series. *Acupunct Med* 2006;24:87–91.
[23] Fu H, Chen B, Hong S, Guo Y. Acupuncture therapy for the treatment of myelosuppression after chemotherapy: a literature review over the past 10 years. *J Acupunct Meridian Stud* 2015;8:122–126.
[24] Mao JJ, Farrar JT, Bruner D, Zee J, Bowman M, Seluzicki C, *et al*. Electroacupuncture for fatigue, sleep, and psychological distress in breast cancer patients with aromatase inhibitor-related arthralgia: a randomized trial. *Cancer* 2014;120:3744–3751.
[25] Mao JJ, Styles T, Cheville A, Wolf J, Fernandes S, Farrar JT. Acupuncture for nonpalliative radiation therapy-related fatigue: feasibility study. *J Soc Integ Oncol* 2009;7:52–58.
[26] Molassiotis A, Bardy J, Finnegan-John J, Mackereth P, Ryder DW, Filshie J, *et al*. Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial. *J Clin Oncol* 2012;30:4470–4476.
[27] Vickers AJ, Straus DJ, Fearon B, Cassileth BR. Acupuncture for postchemotherapy fatigue: a phase II study. *J Clin Oncol* 2004;22:1731–1735.
[28] Hershman DL, Unger JM, Greenlee H, Capodice JL, Lew DL, Darke AK, *et al*. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial. *JAMA* 2018;320:167–176.
[29] Crew KD, Capodice JL, Greenlee H, Brafman L, Fuentes D, Awad D, *et al*. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. *J Clin Oncol* 2010;28:1154–1160.
[30] Frisk J, Kallstrom AC, Wall N, Fredrikson M, Hammar M. Acupuncture improves health-related quality-of-life (HRQoL) and sleep in women with breast cancer and hot flushes. *Support Care Cancer* 2012;20:715–724.
[31] Johnstone PA, Peng YP, May BC, Inouye WS, Niemtzow RC. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2001;50:353–357.
[32] Alimi D, Rubino C, Pichard-Leandri E, Fermand-Brule S, Dubreuil-Lemaire ML, Hill C. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. *J Clin Oncol* 2003;21:4120–4126.
[33] Ezzo J, Vickers A, Richardson MA, Allen C, Dibble SL, Issell B, *et al*. Acupuncture-point stimulation for chemotherapy-induced nausea and vomiting. *J Clin Oncol* 2005;23:7188–7198.
[34] Reindl TK, Geilen W, Hartmann R, Wiebelitz KR, Kan G, Wilhelm I, *et al*. Acupuncture against chemotherapy-induced nausea and vomiting in pediatric oncology. Interim results of a multicenter crossover study. *Support Care Cancer* 2006;14:172–176.
[35] Mao JJ, Bowman MA, Xie SX, Bruner D, DeMichele A, Farrar JT. Electroacupuncture versus gabapentin for hot flashes among breast cancer survivors: a randomized placebo-controlled trial. *J Clin Oncol* 2015;33:3615–3620.
[36] Walker EM, Rodriguez AI, Kohn B, Ball RM, Pegg J, Pocock JR, *et al*. Acupuncture versus venlafaxine for the management of vasomotor symptoms in patients with hormone receptor-positive breast cancer: a randomized controlled trial. *J Clin Oncol* 2010;28:634–640.
[37] Deng G, Vickers A, Yeung S, D'Andrea GM, Xiao H, Heerdt AS, *et al*. Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer patients. *J Clin Oncol* 2007;25:5584–5590.
[38] Lu W, Matulonis UA, Doherty-Gilman A, Lee H, Dean-Clower E, Rosulek A, *et al*. Acupuncture for chemotherapy-induced neutropenia in patients with gynecologic malignancies: a pilot randomized, sham-controlled clinical trial. *J Altern Complement Med* 2009;15:745–753.
[39] Bao T, Iris Zhi W, Vertosick EA, Li QS, DeRito J, Vickers A, *et al*. Acupuncture for breast cancer-related lymphedema: a randomized controlled trial. *Breast Cancer Res Treat* 2018;170:77–87.
[40] Wong W, Chen BZ, Lee AKY, Chan AHC, Wu JCY, Lin Z. Chinese herbal medicine effectively prolongs the overall survival of pancreatic cancer patients: a case series. *Integr Cancer Ther* 2019;18. 1534735419828836.
[41] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, *et al*. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.

[42] Chen BZ, Tian YF. *The diagnosis and Chinese medicine treatment of malignant tumour*. Hong Kong: Wan Li Book Co; 2012.
[43] Morelli MP, Overman MJ, Dasari A, Kazmi SM, Mazard T, Vilar E, *et al*. Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment. *Ann Oncol* 2015;26:731–736.
[44] Liu J, Lin HS, Hou W, Hua BJ, Zhang PT, Li J, *et al*. Comprehensive treatment with Chinese medicine in patients with advanced non-small cell lung cancer: a multicenter, prospective, cohort study. *Chin J Integ Med* 2017;23:733–739.
[45] Jiang Y, Liu LS, Shen LP, Han ZF, Jian H, Liu JX, *et al*. Traditional Chinese Medicine treatment as maintenance therapy in advanced non-small-cell lung cancer: a randomized controlled trial. *Complement Ther Med* 2016;24:55–62.
[46] Chen CM, Lin LZ, Zhang EX. Standardized treatment of Chinese medicine decoction for cancer pain patients with opioid-induced constipation: a multi-center prospective randomized controlled study. *Chin J Integ Med* 2014;20:496–502.
[47] McCulloch M, See C, Shu XJ, Broffman M, Kramer A, Fan WY, *et al*. Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. *J Clin Oncol* 2006;24:419–430.
[48] Shi Z, Song T, Wan Y, Xie J, Yan Y, Shi K, *et al*. A systematic review and meta-analysis of traditional insect Chinese medicines combined chemotherapy for non-surgical hepatocellular carcinoma therapy. *Sci Rep* 2017;7:4355.
[49] Taixiang W, Munro AJ, Guanjian L. Chinese medical herbs for chemotherapy side effects in colorectal cancer patients. *Cochrane Database Syst Rev* 2005:Cd004540.
[50] Sato T, Akiyama M, Nakahama KI, Seo S, Watanabe M, Tatsuzaki J, *et al*. A novel mode of stimulating platelet formation activity in megakaryocytes with peanut skin extract. *J Nat Med* 2018;72:211–219.
[51] Sliva D. Ganoderma lucidum (Reishi) in cancer treatment. *Integ Cancer Ther* 2003;2:358–364.
[52] Khan MA, Tania M, Zhang D, Chen H. Cordyceps mushroom: a potent anticancer nutraceutical. *Open Nutraceut J* 2010;3:179–183.
[53] Nakamura K, Shinozuka K, Yoshikawa N. Anticancer and antimetastatic effects of cordycepin, an active component of Cordyceps sinensis. *J Pharmacol Sci* 2015;127:53–56.
[54] Ma M, Gao X, Qi X, Yu H, Sun S, Wang D. Cordyceps sinensis significantly decreases the radiosensitivity of prostate cancer cells. *Int J Radiat Oncol Biol Phys* 2015;93. E511–E2.
[55] Ma MW, Gao XS, Yu HL, Qi X, Sun SQ, Wang D. Cordyceps sinensis promotes the growth of prostate cancer cells. *Nutr Cancer* 2018;70:1166–1172.
[56] Lam W, Jiang Z, Guan F, Huang X, Hu R, Wang J, *et al*. PHY906(KD018), an adjuvant based on a 1800-year-old Chinese medicine, enhanced the anti-tumor activity of Sorafenib by changing the tumor microenvironment. *Sci Rep* 2015;5:9384.
[57] Lam W, Yang X, Jiang Z, Han X, Guan F, Cheng W, *et al*. Abstract 2724: YIV906 (PHY906) enhanced the antitumor activity of immune checkpoint blockade therapy: anti-PD1 against liver cancer. *Cancer Res* 2018;78:2724.
[58] Saif MW, Li J, Lamb L, Kaley K, Elligers K, Jiang Z, *et al*. First-in-human phase II trial of the botanical formulation PHY906 with capecitabine as second-line therapy in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2014;73:373–380.
[59] Saif MW, Li J, Lamb L, Rosenberg A, Elligers K, Ruta S, *et al*. A phase II study of capecitabine (CAP) plus PHY906 in patients (pts) with advanced pancreatic cancer (APC). *J Clin Oncol* 2009;27:e15508.
[60] Kann BH, Johung K, Cheng Y-C, Lam W, Liu S-H, Decker RH, *et al*. Pilot trial of KD018 with neo-adjuvant concurrent chemo-radiation therapy in patients with locally advanced rectal cancer. *J Clin Oncol* 2017;35. e15162-e.
[61] Teschke R, Zhang L, Long H, Schwarzenboeck A, Schmidt-Taenzer W, Genthner A, *et al*. Traditional Chinese medicine and herbal hepatotoxicity: a tabular compilation of reported cases. *Ann Hepatol* 2015;14:7–19.
[62] Yuen MFL, Sze Hang K. A population based study on the seroprevalence of viral hepatitis in Hong Kong. *Hepatol Int* 2016;10:S207–S208.
[63] Shen T, Liu Y, Shang J, Xie Q, Li J, Yan M, *et al*. Incidence and etiology of drug-induced liver injury in mainland China. *Gastroenterology* 2019;156:2230–2241.
[64] Komoroski BJ, Zhang S, Cai H, Hutzler JM, Frye R, Tracy TS, *et al*. Induction and inhibition of cytochromes P450 by the St. John's wort constituent hyperforin in human hepatocyte cultures. *Drug Metab Dispos* 2004;32:512–518.
[65] Yung T. *Chinese medicine (CM) safety - from scientific evidence to clinical practice*. Hong Kong: Hospital Authority; 2016.
[66] Vincent C, Lewith G. Placebo controls for acupuncture studies. *J R Soc Med* 1995;88:199–202.
[67] Lewith GT, Machin D. On the evaluation of the clinical effects of acupuncture. *Pain* 1983;16:111–127.
[68] Chen H, Yang M, Ning Z, Lam WL, Zhao YK, Yeung WF, *et al*. A guideline for randomized controlled trials of acupuncture. *Am J Chin Med* 2019;47:1–18.
[69] Qi GD, We DA, Chung LP, Fai CK. Placebos used in clinical trials for Chinese herbal medicine. *Recent Pat Inflamm Allergy Drug Discov* 2008;2:123–127.
[70] Fai CK, Qi GD, Wei DA, Chung LP. Placebo preparation for the proper clinical trial of herbal medicine – requirements, verification and quality control. *Recent Pat Inflamm Allergy Drug Discov* 2011;5:169–174.
[71] Leung G. *Effect of Puerarin on Heart Health in Men. 1st ed. US* 2019, https://ClinicalTrials.gov/show/NCT03676296; 2019.
[72] Liu J-P, Chen K-J. Methodology guideline for clinical studies investigating traditional Chinese medicine and integrative medicine: executive summary. *Complement Ther Med* 2015;23:751–756.
[73] Panel on Health Services. *List of outstanding items for discussion. Development of Chinese medicine*. Hong Kong: Legislative Council; 2018.
[74] Lam WC, Zhong L, Liu Y, Shi N, Ng B, Ziea E, *et al*. Hong Kong Chinese medicine clinical practice guideline for cancer palliative care: pain, constipation, and insomnia. *Evid Based Complement Alternat Med* 2019;2019:1038206. https://doi.org/10.1155/2019/1038206.