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Review Article

Concurrent administration of anticancer chemotherapy drug and herbal medicine on the perspective of pharmacokinetics

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ABSTRACT

With an increasing number of cancer patients seeking an improved quality of life, complementary and alternative therapies are becoming more common ways to achieve such improvements. The potential risks of concurrent administration are serious and must be addressed. However, comprehensive evidence for the risks and benefits of combining anticancer drugs with traditional herbs is rare. Pharmacokinetic investigations are an efficient way to understand the influence of concomitant remedies. Therefore, this study aimed to collect the results of pharmacokinetic studies relating to the concurrent use of cancer chemotherapy and complementary and alternative therapies. According to the National Health Insurance (NHI) database in Taiwan and several publications, the three most commonly prescribed formulations for cancer patients are Xiang-Sha-Liu-Jun-Zi-Tang, Jia-Wei-Xiao-Yao-San and Bu-Zhong-Yi-Qi-Tang. The three most commonly prescribed single herbs for cancer patients are *Hedyotis diffusa*, *Scutellaria barbata*, and *Astragalus membranaceus*. Few studies have discussed herb–drug interactions involving these herbs from a pharmacokinetics perspective. Here, we reviewed Jia-Wei-Xiao-Yao-San, Long-Dan-Xie-Gan-Tang, *Curcuma longa* and milk thistle to provide information based on pharmacokinetic evidence for healthcare professionals to use in educating patients about the risks of the concomitant use of various remedies.

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1. Introduction

The use of complementary and alternative medicine (CAM) has been increasing each year, particularly among cancer patients [1]. Up to 52% of cancer patients had used more than one CAM [2], and over 80% of cancer patients use CAM concurrently with chemotherapeutic agents during the initial phases of cancer treatment [3]. Moreover, approximately 50% Chinese cancer patients in North America take herbal prescriptions as assistance [4]. Breast cancer patients are the major potential users of CAM, and followed by prostate and melanoma cancer patients [5]. An interesting study revealed that the source of information on CAM use was friends in 2011 but social media in 2014 [6]. Importantly, the media encourages patients to use herbal medicine to improve their health but rarely educates consumers regarding the potential risks of concomitant use [7]. Therefore, the potential risks and benefits of coadministration of herbal remedies and conventional medicines must be considered. Given comparing the single drug with herbs, their interactions are more complicated and unpredictable than the combination of conventional medicines because of numerous components in herbs [5]. For example, St. John's wort, a notable supplementary, frequently affects the pharmacokinetics of concomitant medicines, such as indinavir, saquinavir, cyclophosphamide, docetaxel, vincristine, etoposide, and irinotecan, most of them are cytochrome P450 enzymes or p-glycoprotein substrates [8,9]. Consequently, the majority of influences are the critical concern by clinicians because the ingested herbs may impact the efficacy and safety of medicines [5]. On the other hand, only 25% cancer patients received the advices from their doctors, even worse they rarely consulted with [10]. Indeed, physicians, medical staff, friends, and families could encourage patients to divulge the daily supplements that they are using. Then, physicians and pharmacists could provide the patients with appropriate information. This review aimed to collect relevant publications and provide medical staff with pharmacokinetics concepts.

2. Strategies of traditional Chinese medicine for cancer patients

Cancer was documented in ancient medical literature as cancerous tissue shaped like a hard stone with a lumpy surface [11]. The first cancer-related record is in an ancient medical book, Huangdi Neijing, which described cancer as a gathering into a permanent massive tumescence [11]. Furthermore, Hau Tuo, the phenomenal Oriental doctor practicing Chinese medicine in the 2nd century, suggested that cancerous lesions located in the internal body should be removed from an anesthetized patient by surgery [12]. Additionally, cancer characteristics, the frequency of lesions in various locations, and sex-specific variations in cancer were recorded in ancient literature. For example, cancer is a lesion that grows deep, similar to a cave, and lesions are typically near one another: cancer is more likely in the abdomen in males, whereas the breast is a highly probable location in females. These ideas were documented in the cancer

occurrence section of Ren Zai Zhi Shi Fu Yi Fang Lun, written by Shiyang Yang.

Given this evidence, cancer has been recorded since the Han dynasty; therefore, cancer has affected human health for over two thousand years. The aim of traditional Chinese medicine is treatment with syndrome differentiation and personalized medicine. Hence, the determination of a suitable strategy for a specific patient depends on the pulse condition and external expression. Chinese medicine doctors have been fighting a long way against cancer with the hope of curing cancer patients, and ancient doctors compiled and documented treatment experiences. These doctors then posited five strategies: nourishing yin and enriching fluid production, clearing heat and detoxication, activating circulation and dissolving stasis, strengthening healthy energy, and combat poison with poison [11,12]. From the modern medicinal perspective, the purpose of nourishing yin and enriching fluid production is to reduce the adverse effects of chemotherapy and radiotherapy, such as nausea, vomiting, mouth ulcers, decreased saliva secretion, oral thirst, dry and painful pharynx, low body temperature, night sweats, and diarrhea, are the exterior syndrome of yin deficiency according to the traditional Chinese medicine theory. Thus, for patients suffering from adverse effects, doctors would focus on reducing the aggravating symptoms and helping them complete their chemotherapy. Some herbs with these benefits are Maidong (*Ophiopogon japonicus*), Shihu (*Dendrobium nobile*), Dangshen (*Codonopsis pilosula*), Xuanshen (*Scrophularia ningpoensis*) and Danshen (*Salvia miltiorrhiza*) [11,12]. Once the cancer grows too fast and large, it stresses the blood flow surrounding tissues. The strategy for this situation is activating circulation and dissolving stasis, as suggested by the literatures [11,12]. Safflower, Danshen, and Chuanxiong (*Ligusticum chuanxiong*) improve circulation, dissolve stasis, inhibit cancer cell proliferation, and reduce the size of the lesion [11,12]. However, if the lesion ulcerates, produces tissue fluid, and causes serious inflammation with pain, the strategy would shift to clearing heat and detoxication. The most common herbs with the ability to clear heat and detoxify are *Taraxacum mongolicum*, *Tripterygium wilfordii*, *Scutellaria barbata*, and *Hedyotis diffusa*, which are also considered against anticancer agents based on clinical studies. The ancient Oriental doctors believed that cancer poisons organs and the body, so they used extreme ways to kill cancerous tissues, such as the use of poison herbs in combating poison. Finally, the most common strategy of traditional Chinese medicine for treating cancer is strengthening healthy energy. This strategy aims to improve a patient's energy and body function and involves tonifying qi before or after cancer therapy by taking ginseng, Huangqi (*Astragalus membranaceus*), and Angelica root (*Angelica sinensis*) [11,12].

3. Contributing factors in herb–drug interactions

Concomitant treatment has an increasing tendency to reduce adverse effects, strengthen immunity, and improve general health, but the potential effects can be positive, negative or neutral when considering the simultaneous use of herbal

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