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From Antiquity to Modernity: Huang Qin Tang at Yale Medical School, Part 3

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Editor's Note: Read part 1 and part 2. The third part of this article on the study of Chinese herbal formula Huang Qin Tang at Yale Medical School looks at the pharmacological research and quality control of the pharmaceutical form of Huang Qin Tang, PHY906.

Pharmacokinetics is the study of the actions of drugs in the body over a period of time. Key elements in the kinetic process include the extent and rate of absorption, distribution, metabolism and excretion. This is abbreviated as ADME and its elements are defined as follows:

- Absorption - the process of a substance entering the blood circulatory system.
- Distribution - the dissemination of substances throughout the fluids and tissues of the body.
- Metabolism - the physical and chemical processes in the body by which the substance is produced, maintained, and destroyed, and by which energy is made available.
- Excretion - the removal of the substances from the body.

This process was investigated in the co-administration of PHY906 with chemotherapeutic agents.[1] PHY906 can enhance the anti-cancer activity of CPT-11 while decreasing CPT-11-induced weight loss and mortality. PHY906 can inhibit the action of multidrug-resistant protein (MDR) and CYP450, thereby facilitating the oral uptake of chemotherapeutic agents. PHY906 potentiates the effect of chemotherapy agents, controls unwanted side-effects of chemotherapy, and does not inhibit the effectiveness of any of the chemotherapeutic agents studied. The effects of PHY906 on the pharmacokinetics of chemotherapy agents such as CTP-11, capecitabine, gemcitabine, and sorafenib have been investigated in studies of colorectal cancer, hepatocellular carcinoma, and pancreatic cancer mice models. These studies have shown that PHY906 does not alter the metabolism of these chemotherapeutic agents or their corresponding metabolites. PHY906 can enhance the antitumor activity of various chemotherapeutic agents and reduce some types of inflammation. PHY906 in combination with CPT-11 can enhance acute pro-inflammatory processes within the tumor. PHY906 inhibits certain receptors which are responsible for diarrhea, vomiting, nausea, and pain.

The investigation of drug-herb interactions deals with the consequences of co-administration of a single herb or herbal formula and a drug. The Yale Project investigated the interactions of PHY906 with CPT-11, 5-FU, LV, Oxaliplatin, Capecitabine, VP-16, L-OddC, Gemcitabine, Sorafenib and Sunitinib. The study of PHY906 on the pharmacokinetics of 5-FU and CPT-11 showed that co-administration of PHY906 along with 5-FU or CPT-11 did not change the pharmacokinetic parameters of 5-FU or CPT-11. Further, the co-administration of PHY906 with CPT-11 did not affect the conversion of CPT-11 to its active metabolite, SN-38. The effects of PHY906 on the pharmacokinetics of capecitabine, gemcitabine, and sorafenib have been studied in colorectal cancer, pancreatic cancer

and hepatocellular carcinoma animal models, respectively.[1] Results consistently showed that PHY906 did not affect the metabolism of these chemotherapeutic agents or their corresponding metabolites. These findings from the Yale Project have been encouragingly positive, and have not noted any adverse reactions.

Both PHY906 and antibiotic treatment inhibited CPT-11-associated inflammatory processes. A study[2] demonstrated that alterations in the population of intestinal bacteria did not affect the abilities of PHY906 to enhance CPT-11 antitumor activity or reduce the intestinal toxicity associated with CPT-11 treatment. The major species of intestinal bacteria do not appear to play a role in PHY906's enhancement of the therapeutic index of CPT-11. Therefore, patients with different intestinal bacterial profiles may still benefit from PHY906 treatment in combination with CPT-11.

Quality Control

Heavy metal tests, microbial tests, and pesticide-residue tests must be conducted in order to determine the safety of an herbal product. In extracting PHY906 from Huang Qin Tang, the industrial standard of Good Manufacturing Practice (GMP) is applied to the production process. The procedures for extracting PHY906 from Huang Qin Tang are summarized as follows:[3]

- 100 mg dried HQT powder is dissolved in 1 mL of 80 degree C water.
- Mixture is subjected to an 80-degree C water bath for 30 minutes and agitated (vortexed) every 10 minutes.
- Mixture is cooled to room temperature in a water bath for 5 minutes.
- Mixture is centrifuged to expel water, resulting in a "supernatant."
- Supernatant is filter-sterilized, leaving a light brown extract.
- Extraction is spray-dried with insoluble dextran, resulting in a granulated powder, and packed in foil.

The Yale Project developed a multi-faceted approach to the quality control of PHY906, including both chemical fingerprints and biological fingerprints of botanicals, and christened the resulting process PhytomicsQC. PhytomicsQC3 integrates four components into the quality control process:

1. High-resolution chemical fingerprint focusing on liquid chromatography/mass spectrometry. To ensure standardization and maintain inter-batch reliability of PHY906, high-performance liquid chromatography was used to establish a "chemical fingerprint" for PHY906.
2. Bio-response fingerprint with genomics technology on differential cellular gene expression was used.
3. Animal pharmacology for in vivo validation was meticulously investigated.
4. Phytomics Similarity Index (PSI), which is a sensitive, quantitative comparison method, was developed to assure the quality consistency of different manufactured batches of PHY906.

Summary

The Yale Project is an inspiring illustration of the potential for East/West integrative medicine in the 21st century. It could be called the regeneration of a new medicine from an ancient prescription. The inventive and entrepreneurial example of the Yale researchers blazes a trail for new biomedical discoveries and new applications of known formulas. Scientists had a history of discovering new medicine from Chinese medicinal herbs. The development of Artemisinin isolated from the plant Artemisia annua (Qing Hao), the single Chinese herb, is an outstanding example of this trend.[4]

Scientists discovered that a low-temperature extraction process could be used to isolate the effective antimalarial substance from the plant. For her role in the discovery and development of antimalarial drug artemisinin, Tu Youyou was awarded the prestigious Lasker-DeBakey Clinical Medical Research Award in 2015.[5] Recently, Tripterygium Wilfordii (Lei Gong Teng) has been intensively studied by researchers led by Dr. Ashok Saluja at the University of Minnesota Masonic Cancer Center. They found that a compound derived from Lei Gong Teng, called triptolide, works to halt the development of HSP 70 (a "survival protein" protecting cancer cells) in tumor cells which makes pancreatic cancer especially aggressive and difficult to treat, since regular chemotherapy drugs do not counteract HSP 70. However, it was difficult to administer triptolide as a drug, because it is not water-soluble. In his laboratory, Dr. Saluja and his team patented a method to create an injectable chemotherapy drug from triptolide, which proved to be highly effective against pancreatic cancer in preclinical trials[6] and ongoing clinical trial.[7]

Yale Project went further from these researches and developments. It took on a whole classical Chinese herbal formula and tapped into the therapeutic power hidden in it. Chinese herbal medicine scholars and practitioners have developed a long list of powerful formulas or prescriptions, which are the gems of traditional Chinese medicine. These formulas and prescriptions have established time-tested records of clinical effectiveness. As we move into a new millennium, we will be wise to consult the wisdom of preceding millennia, exploring the great treasure-trove of classical Chinese herbal formulas for fresh approaches to our health issues.

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