New Pharmacology Inspired by Traditional Chinese Medicine

受中医药启发的新药理学

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Acupuncture was re-introduced to the West after President Richard Nixon's visit to China in 1972. In the 1990s, Luo and Atherton's seminal work on the efficacy of traditional Chinese medicine (TCM) in adult atopic dermatitis[1] catalyzed the global revival of herbal medicine. For the first time in the 50 years of International Union of Basic and Clinical Pharmacology (IUPHAR), there is now a Section on Natural Products, clearly signifying the immense potential of medicines derived from plants and other natural sources. In this presentation, I will discuss some new aspects of pharmacology inspired by recent advances in TCM.

Challenges and opportunities

The challenges in the research and development of TCM are manifold: (1) lack of a common language between TCM and orthodox medicine, (2) composite formulae [*fufang*] of several herbs/minerals are complex, (3) inadequate detection systems for adverse effects, (4) standardization and quality control are major problems, (5) mechanisms of action are largely unknown, and (6) regulation issues in different parts of the world: prescription drugs, botanicals, food supplements, etc. However, the advent of genomics/proteomics/metabonomics offers an ideal opportunity for systematic investigation of TCM.

Modulation of angiogenesis by active compounds from *Panax ginseng* and other Chinese medicinal herbs

Using angiogenesis as a paradigm, we and others have identified both pro-angiogenic and anti-angiogenic components from TCM herbs[2]. Distinct and opposing bioactive compounds can be present simultaneously in a single herb. For example, a mass spectrometric compositional analysis of American, Chinese and Korean, and Sanqi ginseng revealed distinct "sterol ginsenoside" fingerprints, especially in the ratio between a triol, Rg_1, and a diol, Rb_1, the two most prevalent constituents. Our paper[3] "Modulating Angiogenesis – the Yin and the Yang in Ginseng" in *Circulation* (2004) demonstrated that the dominance of Rg_1 leads to angiogenesis, whereas Rb_1 exerts an opposing effect. This paper explained, for the first time, the ambiguity about the effects of ginseng in vascular pathophysiology based on the existence of opposing active principles in the extract. Supporting this hypothesis, Yin *et al*[4] recently showed in a rat model of myocardial infarction that Rg_1 increased the density of newly formed vessels, decreased TNF-α and collagen I expression levels and area of myocardial fibrosis, and improved left ventricle function.

Like *Panax ginseng, Angelica sinensis* (danggui), *Salvia miltiorrhiza* (danshen) and *Astragalus membranaceus* (huangqi) are commonly used TCM. They also contain angiogenesis modulators[5-7]. Interestingly, the metabolism of these medicinal plants by the human gut microbiota can lead to diverse pharmacological activities. For example, ginsenoside metabolites Rh_2, PPD, and PPT significantly enhanced the cytotoxicity of mitoxantrone to human breast carcinoma MCF-7/MX cells which overexpress breast cancer resistance protein (BCRP)[8]. Thus, we need to elucidate the pharmacology of TCM herbs so as to ensure their safe applications in the clinic, and innovate the development of their active components into novel therapeutics.

Molecular targets of TCM herbs as illustrated by ginsenosides

Mechanistically, ginsenoside Rg_1 was found to stimulate angiogenesis through augmenting the production of nitric oxide (NO)[9] and vascular endothelial growth factor (VEGF)[10] via the glucocorticoid receptor. Further studies revealed that such responses were mediated through the PI3K→Akt pathway and PI3K/Akt→GSK3b→b-catenin-TCF pathway, respectively. By contrast, Rb_1 suppressed the formation of endothelial tube-like structures through modulation of pigment epithelium-derived factor (PEDF) via the oestrogen b receptor[11]. These lines of evidence support that the concept that the interaction between ginsenosides and various nuclear steroid hormone receptors may explain the diverse pharmacological activities of ginseng. These findings may also lead to development of more efficacious ginseng-derived therapeutics for angiogenesis-related diseases.

Evidence-based studies to establish the scientific basis of TCM *fufang*

Similar to the current Western combination therapy (polypharmacy) for hypertension and cancer, TCM practitioners have long been using *fufang* to maximize efficacy and minimize adverse effects or toxicity[2].

Zhu Chen and his team[12] in Shanghai Institute of Hematology demonstrated the synergistic effects of the three main active ingredients in the Realgar-*Indigo naturalis*-*Salvia miltiorrhiza* formula for treating human acute promyelocytic leukemia (APL). These chemicals cause stronger reprogramming of myeloid differentiation regulators, and enhanced G_1/G_0 arrest in APL cells through hitting multiple targets compared with the effects of mono- or biagents. Significantly, the mixture facilitates the transportation of tetraarsenic tetrasulfide into APL cells.

More recently, Yung-Chi Cheng and his team[13] at Yale University School of Medicine showed that PHY906, a four-herb *fufang* counteracts gastrointestinal toxicity induced by the chemotherapeutic drug CPT-11 (irinotecan), as shown in a phase I/II clinical study. In a murine colon allograft model, PHY906 increased the antitumor activity of CPT-11. Although PHY906 did not protect against the initial DNA damage and apoptosis triggered by CPT-11 in the intestine, it restored the intestinal epithelium by promoting the regeneration of intestinal progenitor or stem cells. Furthermore, chemical constituents of PHY906 potently inhibited inflammation via several mechanisms that act simultaneously.

Regulation and education

The implementation and enforcement of EU Herbal Directive 2004/24/EC on 1st May 2011 poses a threat to the herbal industry and TCM practitioners as many companies were unable to register their remedies in time. Such regulations will certainly impede the development of TCM in Europe. On the other hand, they will not only provide important educational tool to inform conventional clinicians about the benefits and adverse effects of herbal remedies but also improve quality throughout the product lifecycle from growth and harvest right through to final product and the end user.

On October 31, 2006, the US Food and Drug Administration (FDA) approved the new drug application for marketing of Veregen (sinecatechins), a topical treatment for perianal and genital condyloma. Unlike most small-molecule drugs that comprise a single chemical compound, Veregen, an extract of green tea leaves, contains a mixture of known and possibly active compounds. In their review, Chen *et al*[14] concluded that although new botanical drugs pose many challenges for both industry and the FDA, approval of the first botanical prescription drug shows they can be successfully met. Currently, two TCM *fufang* are undergoing clinical trials in the US for angina (Dantonic®, Danshen Diwan) and liver fibrosis (Fuzheng Huayu).

A European platform to evaluate the R&D of TCM

Following the Sino-European Conference on TCM in Rome in June 2007, a new consortium was established in May 2009 with funds from the European Commission - Good Practice in TCM Research in the Post-genomic Era (GP-TCM; www.gp-tcm.org)[15]. Led by King's College London, GP-TCM is a European Coordination Action with the overall aim to inform best practice and harmonise research of the authentication, quality, safety and efficacy of TCM in EU Member States using a functional genomics approach through exchange of opinions, experience and expertise among scientists in EU Member States and China.

Conclusions

As quality and safety are of paramount importance to the globalisation of TCM, research, funding, regulation and education are equally important. Through cutting-edge research and the harmonization of different pharmacopoeias, we should be able to apply "systems medicine and metabolic phenotyping approaches" (Jeremy K. Nicholson, Imperial College London) to harness the therapeutic potential of potent substances from Nature. As China enters its 12th Five-Year Plan in 2011, there are ample opportunities for clinicians, scientists, biotech and pharma sector in the EU to establish strategic and sustainable collaboration with their Chinese partners in pursuit of healthcare and wellness of mankind.

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References

Sheehan, MP *et al* (1992) Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet*. 340, 13-17.

Fan, TP *et al* (2006) Angiogenesis: from plants to blood vessels. *Trends Pharmacol Sci* 27, 297-309.

Sengupta, S *et al* (2004) Modulating angiogenesis: the yin and the yang in ginseng. *Circulation*, 110,1219-1225.

Yin, H *et al* (2011) Ginsenoside-Rg_1 enhances angiogenesis and ameliorates ventricular remodeling in a rat model of myocardial infarction. *J Mol Med* 89, 363-375.

Yeh, JC *et al* (2011). The natural compound n-butylidenephthalide derived from the volatile oil of Radix *Angelica sinensis* inhibits angiogenesis *in vitro* and *in vivo*. *Angiogenesis* 14, 187-197.

Hur, JM *et al* (2005) Cryptotanshinone but not tanshinone IIA inhibits angiogenesis *in vitro*. *Exp Mol Med* 37, 133-137

Tang, JY *et al* (2010) Calycosin promotes angiogenesis involving estrogen receptor and mitogen-activated protein kinase (MAPK) signaling pathway in zebrafish and HUVEC. *PLoS One*, 5(7):e11822.

Jin, J *et al* (2006) Metabolites of ginsenosides as novel BCRP inhibitors. *Biochem Biophys Res Commun* 345,1308-14.

Leung, KW *et al* (2006) Signaling pathway of ginsenoside Rg_1 leading to nitric oxide production in endothelial cells. *FEBS Letters* 580, 3211-3216.

Leung, KW *et al* (2006) Ginsenoside-Rg_1 induces vascular endothelial growth factor expression through the glucocorticoid receptor-related phosphatidylinositol 3-kinase/Akt and b-catenin/T-cell factor-dependent pathway in human endothelial cells. *J Biol Chem* 281, 36280-36288.

Leung, KW *et al* (2007) Ginsenoside Rb_1 inhibits tube-like structures formation of endothelial cells by regulating pigment epithelium-derived factor through the oestrogen b receptor. *Br J Pharmacol* 152, 207-215.

Wang, L *et al* (2008). Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia. *Proc Natl Acad Sci U S A* 105, 4826-4831.
Lam, W *et al* (2010) The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. *Sci Transl Med* 2, 45ra59.
Chen, ST *et al* (2008) New therapies from old medicines. *Nature Biotechnology* 26, 1077-1083.
Uzuner, H *et al* (2010) Establishing an EU-China consortium on traditional Chinese medicine research. *Chinese Medicine* 5:42