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Molecular network and chemical fragment-based characteristics of medicinal herbs with cold and hot properties from Chinese medicine

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ABSTRACT

Ethnopharmacological relevance: Chinese herbal medicines (HMs) is one of the great herbal systems of the world, which play an important role in current health care system in many countries. In the view of tradition Chinese medicine (TCM) theory, Yin-yang and five-elements theory is the central theory, which is used to explain how the world and body work. Under the guidance of such philosophy, TCM considers that HMs have different properties, which are the important factors for prescribing herbal formulae; such prescriptions are based on TCM pattern classification in clinical practice. The cold and hot property are commonly defined for HM property identification; however, the biological activities that are related to the HM property remain a mystery because of a lack of appropriate methods. A bioinformatics approach was applied to identify the distinguishing biological activities of HMs that have these cold and hot properties.

Material and methods: Twenty HMs with typical cold and hot properties (10 cold and 10 hot) were selected based on TCM clinical application records and Chinese pharmacopeia. The active target proteins of each HM were searched in the PubChem database and were analyzed in Ingenuity Pathway Analysis (IPA) platform to find out the HM property-related biological activities. In addition, the main compounds of the HMs were fragmented using a fragment-based approach and were analyzed for the purpose of deciphering the properties.

Results: The main biological networks of HMs with cold and hot properties include cell cycle, cellular growth, proliferation and development, cancer, cytokine signaling, and intracellular and second messenger signaling; 11 specific pathways are presented to be perturbed only by HMs with the hot property, and the 27 specific target protein molecules include PRKACA, PRKCA, PRKCB, PRKCD, PRKCE, PRKCG, PRKD1, TLR4, TLR7, TLR8, TLR9, HTR4, HTR6, HTR7, HTR2A, HTR1B, HTR2B, GNAO1, GNAI1, TNF, IL8, ROCK2, AKT1, MAPK1, RPS6KA1, RPS6KA3 and JAK2, which are involved in the biological network. One specific pathway is detected to be involved in the biological network of HMs with the cold property, the specific molecules are RAN and KPNB1. Cold propertied HMs show intensive toxicity in the heart, liver and kidney compared with hot HMs, which is likely to be correlated with the specific chemical fragments constructions in the HMs with the cold property, such as long chain alkenes, Benzo heterocycle and azotic heterocycle according to the chemical fragment analysis for the HMs.

Conclusions: Inflammation and immunity regulation are more related to HMs with the hot property, and cold propertied HMs possess the tendency to impact cell growth, proliferation and development. Integrative bioinformatics analysis and chemical structure analysis are a promising methods for identifying the biological activity of HM properties.

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1. Introduction

Traditional Chinese medicine (TCM), which encompasses many different practices, is rooted in the ancient philosophy of Taoism and dates back thousands of years. Today, TCM has been widely practiced and is considered to be an important complementary and alternative medical system worldwide (Jiang et al., 2011b). Underlying the practice of TCM there is a unique view of the world and the human body that is different from Western medicine concepts. This view is based on the ancient Chinese philosophy, and the theoretical framework of TCM include Yin-yang and five elements theory, these concepts represented the opposing yet complementary and corresponding aspects of the world and life. Based on these theory, TCM considers that Chinese herbal medicines (HMs) have different properties, which are the important factors for prescribing herbal formulae; prescriptions are chosen based on TCM pattern classification in clinical practice (Xiao, 2008; Zhou et al., 2004).

Each drug is regarded to have its own specific characteristics, such as properties and flavors (Sheng, 2004). The four main properties refers to the cold, hot, warm, or cool nature of Chinese herbs and can be summed up as cold and hot (Yu et al., 2006; Long et al., 2011). The cold and hot properties are believed to mainly originate from the reactions of the body to a specific HM, for example, it is common sense that chewing a mint leaf causes a cold feeling, while masticating a piece of ginger root is associated with a hot sensation (Zhao et al., 2011). The properties of HM are first considered by their relationship with the environmental temperature and the body feelings in relation to the environment (Zhao et al., 2011), then, the theory is extended to the HMs that do not have obvious temperature features yet can induce similar reactions in the human body. In general, herbs with the cold property are believed to clear away hot, remove toxic substances and nourish yin, and are used to cure hot syndromes, such as a hyper-reaction of the sympathetic nervous and adrenergic system; in contrast, herbs with the hot property usually warm up the interior, dispel cold and support yang, and are therefore used to treat cold syndromes, such as a hypo-reaction of the nervous system (Liu et al., 2008).

However, until now it has been difficult to find a scientific way to prove and characterize the so-called cold and hot properties of herbal drugs as highly abstracted HM theory (Li et al., 2010). Many studies have been developed that attempt to unlock the myth of the cold/hot properties of HMs. Some findings have been documented for changes that are associated with the cold or hot properties of herbal drugs, such as the predictive system of the cold/hot property of HMs based on a chemical materials basis (Long et al., 2011); the temperature tropism of animals energy metabolism or biothermodynamics (Jia et al., 2010; Yang et al., 2010; Zhao et al., 2011); animal thermotropism behavior surveillance (Zhao et al., 2011); and the observation to the plain herbs in vitro (Sui et al., 2010; Wang et al., 2009).

Table 1
Selected typical Chinese herbal medicines.

Properties	Chinese name	Latin name	Family	Genus
Cold	Da Huang	*Rheum palmatum* L.	Polygonaceae	Rheu
	Long Dan	*Gentiana scabra* Bunge	Gentianaceae	Gentiana
	Zhi Zi	*Gardenia jasminoides* Ellis	Rubiaceae	Gardenia
	Huang Bai	*Cortex Phellodendri* Chinensis	Rutaceae	Phellodendron
	Huang Lian	*Coptis chinensis* Franch	Ranunculaceae	Coptis
	Huang Qin	*Scutellaria baicalensis* Georgi	Labiatae	Scutellaria
	Ku Shen	*Sophora flavescens*	Leguminosae	Sophora
	Ban Lan Gen	*Isatistinctoria* L.	Cruciferae	Isatis
	Da Qing Ye	*Isatis indigotica* Fort	Cruciferae	Isatis
	Shan Dou Gen	*Radix sophorae tonkinesis*	Leguminosae	Sophora
Hot	Ba Dou	*Fructus Crotonis*	Euphorbiaceae	Croton
	Bi Ba	*Piper longum* L.	Piperaceae	Piper
	Chuan Wu	*Aconitum carmichaelii*	Ranunculaceae	Aconitum
	Fu Zi	*Aconitum napellus*	Ranunculaceae	Aconitum
	Gan Jiang	*Zingiber officinale* Roscoe	Zingiberaceae	Zingiber
	Xian Mao	*Rhizoma Curculiginis*	Hypoxidaceae	Curculigo
	Hu Jiao	*Piper nigrum* L.	Piperaceae	Piper
	Rou Gui	*Cinnamomi Cassiae*	Lauraceae	Cinnamomum
	Wu Zhu Yu	*Evodia rutaecarpa*	Rutaceae	Tetradium
	Gao Liang Jiang	*Rhizoma Alpiniae Officinarum*	Zingiberaceae	Alpinia

Table 2
Top 5 of the cold and hot HMs related networks.

ID	Top 5 networks of HMs with cold property		Top 5 networks of HMs with hot property	
	Associated network functions	Score	Associated network functions	Score
1	DNA replication, recombination and repair cell cycle *cellular assembly and organization*	40	Cell death and survival cell cycle DNA replication, recombination and repair	38
2	Lipid metabolism small molecule biochemistry endocrine system development and function	38	*Cancer endocrine system disorders* lipid metabolism	34
3	*Cellular movement hematological system development and function* immune cell trafficking	27	Endocrine system development and function lipid metabolism small molecule biochemistry	34
4	Cell death and survival DNA replication, recombination and repair *tumor morphology*	26	*Cancer gene expression cellular development*	34
5	*Cell morphology connective tissue development and function cell signaling*	26	*Inflammatory response* DNA replication, recombination and repair cell death and survival	26

Italic words indicate the distinguishing parts.

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