DOI: 10.1002/cmdc.200700291

How Many Traditional Chinese Medicine Components Have Been Recognized by Modern Western Medicine? A Chemoinformatic Analysis and Implications for Finding Multicomponent Drugs

De-Xin Kong, Xue-Juan Li, Guang-Yan Tang, and Hong-Yu Zhang*[a]

Traditional Chinese medicine (TCM), featured in its combinatorial use of herbs (sometimes animals and minerals are also involved), has been developed in China for more than 4000 years. Although TCM attracts more and more attention from medicinal practice throughout the world and is considered a promising source of new drugs,[1–7] it is still outside mainstream medicine, because of the conceptual differences between TCM therapy and modern medication. However, it should be pointed out that historically Western medicine also depended on natural products (for over 3000 years) and synthetic modern drugs only began to blossom approximately 100 years ago.[8,9] In addition, it is estimated that ~50% of currently used modern Western drugs are derived from natural products.[9–12] Considering the fact that the plant distribution patterns in China and Western countries are rather similar, it is reasonable to infer that there exist certain similarities between TCM components and modern Western drugs and some TCM components may have been recognized by modern Western medicine, although by and large both medical systems evolved independently. To verify this speculation, we employed chemoinformatic methods to make a global structural comparison between the two kinds of drugs.

Structurally similar agents in TCM and modern Western medicine

In the present analysis, traditional Chinese medicine database (TCMD),[13] which records 10458 components extracted from 4636 TCMs (including herbs, animals, and minerals) and the comprehensive medicinal chemistry (CMC) database,[14] which contains 8659 approved modern drugs (of which 7988 molecules are represented in Mol2 format), were used as data sources of TCM components and modern Western drugs, respectively. The molecular similarity comparison of TCMD and CMC database was performed by using atom environment descriptors (MOLPRINT 2D).[15] As a result, 908 TCMD–CMC agent pairs were found to be structurally similar (with similarity $>85\%$) and 327 agents were revealed as common members of both databases, which indicates that a certain part of TCM components have been recognized by modern Western medicine. As the structurally identical agents are of special interest to our study, they are listed in Table S1 and are analyzed in detail (see below).

Western-medicine-justified TCMs

According to the annotation of TCMD, the 327 agents common to both TCMD and CMC are owned by 1186 TCMs. It is of great interest to explore whether the TCMs containing these agents show the same activity as the corresponding CMC drugs. However, one should bear in mind that in TCMD a large part of TCM activities are expressed in modern pharmacological terms. To guarantee the creditability of the present investigation, we prefer to examine anciently recorded pharmacological effects of TCMs. As is widely known, the ancient TCM activities were expressed in a unique Chinese medicinal conceptual system and can not be completely translated into Western medicinal concepts. Nevertheless, some Western pharmacological terms (such as analgesic, anthelmintic, antiasthmatic, antihemorrhagic, antimalarial, antipruritic, antipyretic, antiseptic, antispasmodic, antitussive, astringent, dermatologic, detoxicant, diuretic, emetic, hematopoietic, hemostatic, hepatoprotective, insecticide, laxative, parasiticide, pediculicide, scabicide, and vulnerary) have similar meanings in ancient Chinese medicinal system. Thus, these activity categories were considered to explore how many TCMs have been validated by modern Western medicine.

As shown in Table S2, more than 100 TCMs display the same pharmacological effects (recorded in ancient Chinese medicinal books) as the agents contained in the CMC. For instance, 17 herbs (such as Wang Jiang Nan, Hu Zhang, and Fan Xie Ye) containing CMC laxative agents (for example, danthron, emodin, and sennosides A + B) are also annotated as laxatives, 13 plants (such as Zang Qie, Yang Jin Hua, and Lang Dang Zi) containing CMC antispasmodic agents (such as anisodamine, scopolamine, and hyoscyamine) also exhibit antispasmodic activity and 14 plants (such as Xiong Guo, Ke Ke, and Mao Di Huang) containing CMC diuretic agents (such as arbutin, theobromine, and gitoxin) are indeed defined as diuretic. Moreover, it is somewhat surprising to note that a part of Western-medicine-validated TCM pharmacological effects have been identified ~1500 years ago (Table 1). All of this evidence suggests that TCM, at least in part, has a scientific basis.

Considering the fact that only a small part of TCM components have been identified and the agents recorded in CMC does not represent all Western drugs, we think that the pres-

[a] Dr. D.-X. Kong, X.-J. Li, G.-Y. Tang, Prof. H.-Y. Zhang
Shandong Provincial Research Center for Bioinformatic Engineering and Technique
Center for Advanced Study
Shandong University of Technology
Zibo 255049 (P. R. China)
Fax: (+86) 533-278-2071
E-mail: zhanghy@sdut.edu.cn

Supporting information for this article is available on the WWW under http://www.chemmedchem.org or from the author.

Table 1. Anciently used TCMs justified by Western medicine.

Herb name/Species	Source	Activity[f]	CMC agents[g]
Bai He/*Lilium brownii var. viridulum*	*Ben Jing*[a]	Laxative	Emodin
Ban Xia/*Pinellia ternata*	*Ben Jing*[a]	Analgesic	Cicutine
Bin Lang/*Areca catechu*	*Ming Yi Bie Lu*[b]	Anthelmintic	Arecoline
Cha Ye/*Camellia sinensis (leaf)*	*Shen Nong Shi Jing*[c]	Diuretic	Caffeine
			Theobromine
Chan Chu/*Bufo bufo gargarizans*; *Bufo melanostictus*	*Si Min Yue Ling*[d]	Dermatologic	Cinobufagin
Chao Xian Yin Yang Huo/*Epimedium koreanum*	*Ben Jing*[a]	Laxative	Emodin
Da Huang/*Rheum officinale*	*Ben Jing*[a]	Laxative	Emodin
			Sennosides A + B
Dang Gui/*Angelica sinensis*	*Ben Jing*[a]	Dermatologic	Azelaic acid
Gan Di Huang/*Rehmannia glutinosa*	*Ming Yi Bie Lu*[b]	Diuretic	Mannitol
Gao Liang Jiang/*Alpinia officinarum*	*Ming Yi Bie Lu*[b]	Analgesic	Eugenol
Guang Huo Xiang/*Pogostemon cablin*	*Ming Yi Bie Lu*[b]	Analgesic	Eugenol
Huang Bai/*Phellodendron amurense*	*Ben Jing*[a]	Antipyretic	Berberine sulfate
Huang Hao/*Artemisia scoparia*	*Ming Yi Bie Lu*[b]	Dermatologic	Azelaic acid
			Salicylic acid
	Ben Jing[a]	Laxative	Emodin
Huang Hua Hao/*Artemisia annua*	*Ben Jing*[a]	Dermatologic	Salicylic acid
		Anthelmintic	Santonin
Huang Lian/*Coptis chinensis*	*Ben Jing*[a]	Antipyretic	Berberine sulfate
Ji Zi Bai/*Gallus gallus domesticus*	*Ming Yi Bie Lu*[b]	Analgesic	Aminobenzoic acid
Jue Ming Zi/*Cassia tora(seed)*	*Ben Jing*[a]	Laxative	Emodin
Kuan Ye Xiang Pu/*Typha latifolia*	*Ben Jing*[a]	Antihemorrhagic	Quercetin
Lang Dang Zi/*Hyoscyamus niger (seed)*	*Ming Yi Bie Lu*[b]	Antispasmodic	Atropine
			Scopolamine
			Apoatropine
Luo Le/*Ocimum basilicum*	*Ming Yi Bie Lu*[b]	Analgesic	Eugenol
Pu Huang/*Typha angustata*	*Ben Jing*[a]	Diuretic	Mannitol
		Antihemorrhagic	Quercetin
Qing Jiao/*Zanthoxylum schinifolium*	*Ben Jing*[a]	Dermatologic	5-Methoxypsoralen
Shi Liu Gen/*Punica granatum(root)*	*Ming Yi Bie Lu*[b]	Anthelmintic	Isopelletierine
Tang Gu Te Da Huang/*Rheum tanguticum*	*Ben Jing*[a]	Laxative	Emodin
			Sennosides A + B
Xi Xin/*Asarum sieboldii*	*Ben Jing*[a]	Analgesic	Eugenol
Xia Ye Xiang Pu/*Typha angustifolia*	*Ben Jing*[a]	Antihemorrhagic	Quercetin
Xian He Cao Gen Ya/*Agrimonia pilosa var. japonica(root and bud)*	*Ben Jing*[a]	Anthelmintic	Agrimophol
Xin Yi/*Magnolia liliflora*	*Ben Jing*[a]	Analgesic	Eugenol
Yin Chen Hao/*Artemisia capillaris*	*Ben Cao Jing Ji Zhu*[e]	Analgesic	Eugenol
Zhang Ye Da Huang/*Rheum palmatum*	*Ben Jing*[a]	Laxative	Danthron
			Emodin
			Sennosides A + B
Zi Yu Lan Hua/*Magnolia liliflora (flower)*	*Ben Jing*[a]	Analgesic	Eugenol

[a] Anonymous, written in Eastern Han Dynasty (25 AD ~220 AD). [b] written by Tao Hong-Jing in Liang Dynasty (502 AD ~536 AD). [c] Anonymous, written in Eastern Han Dynasty (25 AD ~220 AD). [d] written by Cui Shi from 130 AD to 180 AD. [e] written by Tao Hong-Jing in Liang Dynasty (502 AD ~536 AD). [f] recorded in the corresponding Chinese medicinal books. [g] CMC agents contained in the TCM, which show the same activity as the TCM.

ently revealed Western-medicine-justified TCMs are the tip of the iceberg. In fact, some of the well-known TCM herbs are not included in the present analysis. For instance, Qing Hao (*Artemisia annua*), which has been recorded in an ancient Chinese medicinal book, Zhou Hou Bei Ji Fang (written by Ge Hong at about 341 AD) and has derived a very efficient antimalarial agent Qing Hao Su (artemisinin),[16] is not contained in the present screening. Therefore, it can be expected that with increased knowledge of TCM and Western drugs, more and more evidence will be accumulated to justify TCM.

Implications for finding Western drug combinations

The present findings not only help to understand the scientific basis of TCM but also have important implications for drug discovery, especially for finding Western drug combinations. The pharmaceutical industry is facing an unprecedented challenge: more funds are invested, but less new drugs are generated.[17,18] This predicament is partially attributed to the limitations of the current one-drug-one-target paradigm in drug discovery.[17,18] Thus, more and more attention is given to multicomponent therapeutics which incorporates two or more active ingredients in one drug to hit multiple targets.[8,19–21] Nevertheless, it is a huge challenge to select appropriate agents to combine, because of the explosive number increase of drug combinations, the potential risks of drug–drug interactions and the unpredictable pharmacokinetic properties of multiple components.[22,23] Considering the facts that: 1) traditional Chinese therapeutics has accumulated rich experience in combinations of herbs and other natural materials (for exam-

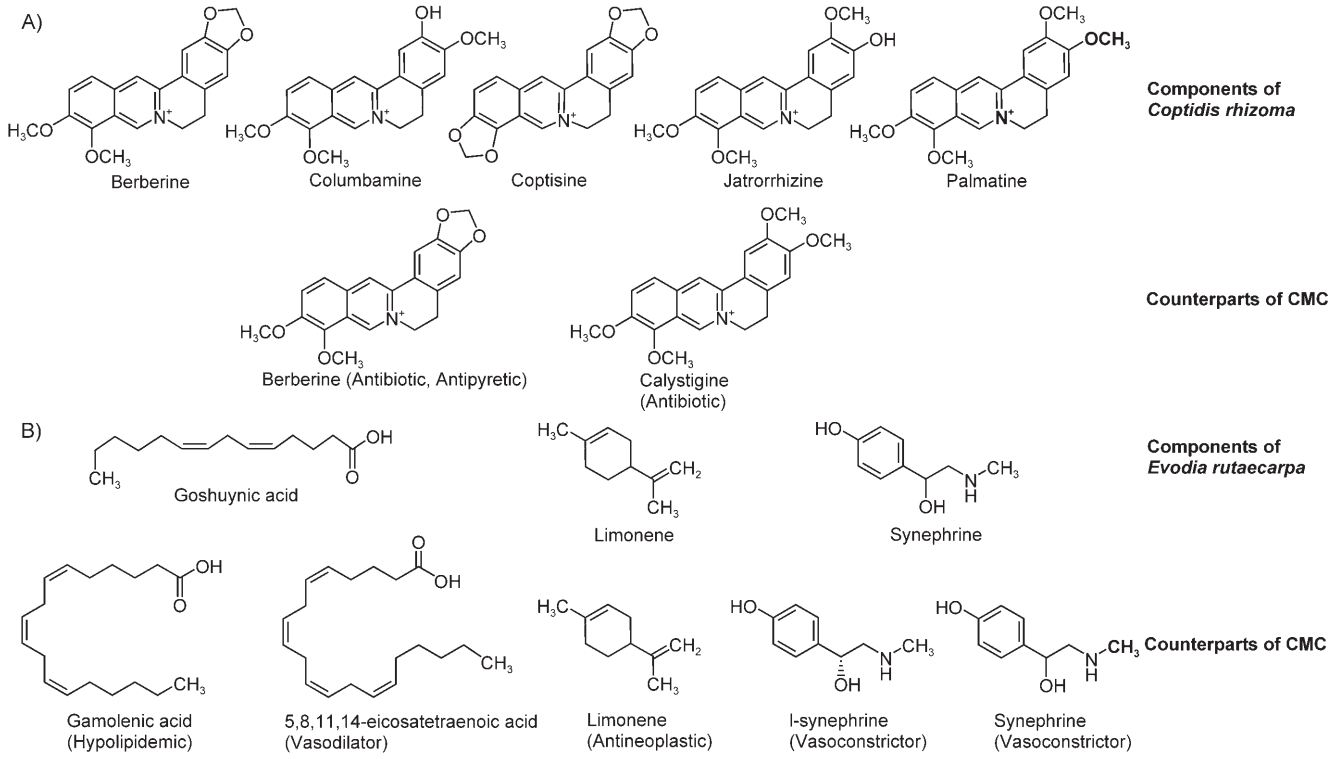

Figure 1. Some components of A) *Coptidis rhizoma* and B) *Evodia rutaecarpa* with corresponding CMC counterparts (with structural similarity $>85\%$).

ple, more than 100 000 formulae have been recorded in TCM)[24] and 2) a certain part of Western drugs are structurally similar to TCM components (as described above), we speculate that it is possible to use TCM formulae to direct the combination of Western drugs by taking advantages of reducing the number of drug combinations and lowering the potential risks of drug–drug interactions and complex pharmacokinetic behaviors of diverse components.

This new strategy will begin with identifying the commonly used TCM combinations, aiming at certain diseases, from hundreds of thousands of TCM formulae. Then, the components of the TCM combinations can be collected through searching TCMD or other TCM databases and the Western drug counterparts of the TCM components can be obtained by structural similarity searching in CMC or other Western drug databases. From the annotated activities of the Western drugs, one can make some preliminary judgements on the feasibility of the potential Western drug combinations and finally evaluate the promising ones by pharmacological experiments. An example to execute this strategy is given below.

Coptidis rhizoma and *Evodia rutaecarpa* are commonly combined in TCM to treat gastric conditions (in fact, this is a very efficacious herb couple to inhibit *Helicobacter pylori*). Recently, it was revealed that the extracts of this herb combination can reverse the changes in metabolism of rats that were given 1,2-dimethylhydrazine to induce tumors in their colons.[24] Through searching TCMD, 12 and 45 components were identified for *Coptidis rhizoma* and *Evodia rutaecarpa*, respectively (Tables S3 and S4). By comparing the structures of these components with those recorded in the CMC database, some Western drug counterparts (with structural similarity $>85\%$) were obtained (Figure 1). It is interesting to note that one of the retrieved CMC drugs (limonene) is annotated as antineoplastic and some others, such as calystigine, berberine (antibiotics, the latter is a potential *Helicobacter pylori* inhibitor[25]), and gamolenic acid (hypolipidemic), are also relevant for antitumor treatment.[26,27] Thus, it will be of interest to evaluate the anticancer effects (especially for tumors in the digestive system) of the combinations that contain limonene and one or more other agents (such as, calystigine, berberine, and gamolenic acid). Moreover, TCM is also a rich potential source of multidrug resistance (MDR) inhibitors.[7] For instance, rutecarpine, an alkaloid derived from *Evodia rutaecarpa*, is a potent MDR modulator.[28] Recently, Min et al. revealed that obacunone, which is contained in both *Coptidis rhizoma* and *Evodia rutaecarpa* (Tables S3 and S4), showed significant P-glycoprotein MDR inhibitory activity in the human MDR uterine sarcoma cell line MES-SA/DX5 and human colorectal cancer cell line HCT15.[29] These findings not only offered new clues to explaining the anticancer potential of the herbs, but also suggested that rutecarpine and/or obacunone may be considered as components of anticancer multicomponent drugs.

In summary, TCM has been used for more than 4000 years and has made great contributions to maintaining the health of Chinese. However, the effectiveness of TCM has not been fully recognized. The present global comparison between TCM components and modern Western drugs indicates that a certain part of TCM components have been recognized by modern Western medicine. Moreover, some TCMs are justified by Western medicine, interestingly some of which have been

recorded in very ancient (~1500 years ago) Chinese medicinal books. All of these findings suggest that TCM, at least in part, has a scientific basis. Therefore, TCM is promising to derive new drugs and to help find novel Western drug combinations as well.

Acknowledgements

This study was supported by the National Basic Research Program of China (grant 2003CB114400) and the National Natural Science Foundation of China (grant 30570383).

Keywords: chemoinformatics · drug discovery · multicomponent therapeutics · traditional Chinese medicine · western medicine

[1] K. Chan, *Trends Pharmacol. Sci.* **1995**, *16*, 182–187.
[2] R. Yuan, Y. Lin, *Pharmacol. Ther.* **2000**, *86*, 191–198.
[3] N. Wiseman, *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 445–455.
[4] M. W. Wang, X. J. Hao, K. X. Chen, *Philos. Trans. R. Soc. London Ser. B* **2007**, *362*, 1093–1105.
[5] B. M. Schmidt, D. M. Ribnicky, P. E. Lipsky, I. Raskin, *Nat. Chem. Biol.* **2007**, *3*, 360–366.
[6] T. Efferth, P. C. H. Li, V. S. B. Konkimalla, B. Kaina, *Trends Mol. Med.* **2007**, *13*, 353–361.
[7] X.-J. Li, H.-Y. Zhang, *Trends Mol. Med.* **2008**, *14*, in press.
[8] C. T. Keith, A. A. Borisy, B. R. Stockwell, *Nat. Rev. Drug Discovery* **2005**, *4*, 71–78.
[9] D. J. Newman, G. M. Cragg, K. M. Snader, *Nat. Prod. Rep.* **2000**, *17*, 215–234.
[10] D. J. Newman, G. M. Cragg, K. M. Snader, *J. Nat. Prod.* **2003**, *66*, 1022–1037.
[11] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461–477.
[12] M. S. Butler, *Nat. Prod. Rep.* **2005**, *22*, 162–195.
[13] Traditional Chinese Medicine Database (TCMD), Accelrys Inc., Beijing, Chinese edition, **2005** (http://www.neotrident.com/newpage/show_page.asp?ArticleID=973&ClassID=112&GroupID=26).
[14] Comprehensive Medicinal Chemistry (CMC), MDL Information Systems Inc., San Leandro, CA(USA), **2004** (http://www.mdl.com).
[15] A. Bender, H. Y. Mussa, R. C. Glen, S. Reiling, *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1708–1718.
[16] M. A. van Agtmael, T. A. Eggelte, C. J. van Boxtel, *Trends Pharmacol. Sci.* **1999**, *20*, 199–205.
[17] L. K. Buehler, *PharmaGenomics* **2004**, *4*, 24–26.
[18] R. R. Ruffolo, *Expert Opin. Drug Discovery* **2006**, *1*, 99–102.
[19] J. B. Fitzgerald, B. Schoeberl, U. B. Nielsen, P. K. Sorger, *Nat. Chem. Biol.* **2006**, *2*, 458–466.
[20] G. R. Zimmermann, J. Lehár, C. T. Keith, *Drug Discovery Today* **2007**, *12*, 34–42.
[21] H. Kitano, *Nat. Rev. Drug Discovery* **2007**, *6*, 202–210.
[22] R. Morphy, C. Kay, Z. Rankovic, *Drug Discovery Today* **2004**, *9*, 641–651.
[23] R. Morphy, Z. Rankovic, *J. Med. Chem.* **2005**, *48*, 6523–6543.
[24] J. Qiu, *Nature* **2007**, *448*, 126–128.
[25] E. A. Bae, M. J. Han, N. J. Kim, D. H. Kim, *Biol. Pharm. Bull.* **1998**, *21*, 990–992.
[26] N. Shimizu, Y. Ikehara, K.-I. Inada, H. Nakanishi, T. Tsukamoto, K. Nozaki, M. Kaminishi, S. Kuramoto, A. Sugiyama, T. Katsuyama, M. Tatematsu, *Cancer Res.* **2000**, *60*, 1512–1514.
[27] L. M. Berstein, *Cancer Lett.* **2005**, *224*, 203–212.
[28] C. Avendaño, J. C. Menéndez, *Curr. Med. Chem.* **2002**, *9*, 159–193.
[29] Y. D. Min, H. C. Kwon, M. C. Yang, K. H. Lee, S. U. Choi, K. R. Lee, *Arch. Pharmacal Res.* **2007**, *30*, 58–63.

Received: October 13, 2007
Published online on November 19, 2007

