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Application of transcriptomics in Chinese herbal medicine studies

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Abstract

Transcriptomics using DNA microarray has become a practical and popular tool for herbal medicine study because of high throughput, sensitivity, accuracy, specificity, and reproducibility. Therefore, this article focuses on the overview of DNA microarray technology and the application of DNA microarray in Chinese herbal medicine study. To understand the number and the objectives of articles utilizing DNA microarray for herbal medicine study, we surveyed 297 frequently used Chinese medicinal herbs listed in Pharmacopoeia Commission of People's Republic of China. We classified these medicinal herbs into 109 families and then applied PudMed search using "microarray" and individual herbal family as keywords. Although thousands of papers applying DNA microarray in Chinese herbal studies have been published since 1998, most of the articles focus on the elucidation of mechanisms of certain biological effects of herbs. Construction of the bioactivity database containing large-scaled gene expression profiles of quality control herbs can be applied in the future to analyze the biological events induced by herbs, predict the therapeutic potential of herbs, evaluate the safety of herbs, and identify the drug candidate of herbs. Moreover, the linkage of systems biology tools, such as functional genomics, transcriptomics, proteomics, metabolomics, pharmacogenomics and toxicogenomics, will become a new translational platform between Western medicine and Chinese herbal medicine.

Keywords: Transcriptomics, DNA microarray, Chinese herbal medicine

Introduction

Systems biology employing omics as research tools has been used for Chinese herbal medicine study. Omics, such as functional genomics, transcriptomics and proteomics, can be applied to study the gene/protein functions of medicinal herbs and to evaluate the herb/host interactions. Moreover, metabolomics, pharmacogenomics, and toxicogenomics can be utilized to examine the chemical processes involving metabolites of medicinal herbs, to investigate the variations within the host genome and herbs, and to analyze the toxic effects of herbs (Barlow et al., 2012; Buriani et al., 2012; Hsiang et al., 2009; Kuete and Efferth, 2011; Pelkonen et al., 2012; Sertel et al., 2012; Youns et al., 2010). Transcriptomics using DNA microarray has become a practical and popular tool for herbal medicine study because of high throughput, sensitivity, accuracy, specificity, and reproducibility. Thousands of papers applying DNA microarray in Chinese herbal

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study have been published since 1998. Therefore, this article focuses on the overview of DNA microarray technology and the application of DNA microarray in Chinese herbal medicine study. Furthermore, the linkage of systems biology tools and its application as a new translational platform between Western medicine and Chinese herbal medicine are discussed.

An overview of DNA microarray technology

Microarray technology was created by Dr. Schena and his colleagues at Stanford University in 1995 (Schena et al., 1995). They published the first paper on the use of cDNA microarray probes that were printed in a two-dimensional grid onto glass slides. In 1996, Affymetrix began to market commercially available DNA chips. Various microarray experimental platforms have been developed since then. Two major types of microarray platforms are used now. Spotted microarrays utilize oligonucleotides, cDNA, or small fragments of polymerase chain reaction products that correspond to mRNAs as the probes. The probes are synthesized on the array surface and then spotted onto glasses (Schena et al., 1995). Oligonucleotide microarrays, on the other hand, use short oligonucleotide probes designed to match parts of open reading frames. Oligonucleotide microarrays are produced by printing probes directly onto the array surfaces or by photolithographic synthesis of probes on silica substrates (Lipshutz et al., 1999). Oligonucleotide microarrays are the most widely used platforms in basic and applied researches (Joos and Kroeger, 2008).

DNA microarray platform provides a high-throughput approach that enables researchers to monitor the expression of thousands of genes simultaneously. However, the intra- and inter-platform consistency of these platforms has been issued (Draghici et al., 2006). Standardizing global gene expression analysis between laboratories and across platforms can overcome these problems (Bammler et al., 2005). The standardized protocols include sample preparation, RNA isolation, amplified RNA (aRNA) synthesis, hybridization, and data analysis. The quality control check point for microarray experiment has also been established. For examples, the criteria for RNA sample include RNA concentration and purity. If the integrity number of RNA is more than eight, it means RNA is suitable for aRNA synthesis. The criteria for aRNA labeling include concentration and incorporation efficiency. If the incorporation efficiency is 30-60 dye molecules per 1,000 nucleotides, it means aRNA labeling is suitable for hybridization. The whole-gene expression profile according to the standardized protocol can yield data that are consistent between laboratories and are intrinsically comparable (Brazma et al., 2001; Knapen et al., 2009; Slonim and Yanai, 2009). In addition, comparison of the biological function instead of the list of differentially expressed genes can also overcome the inconsistency between different platforms (Li et al., 2009).

DNA microarray technology applied in Chinese herbal medicine study

To overview the application of DNA microarray technology in Chinese herbal medicine study, we survey the number and objectives of papers dealing with frequently used Chinese medicinal herbs and their constituents, and further summarize how to utilize microarray in herbal research. The well-knowing or commonly used herbs and herbal compounds, such as Three Yellows Heart-Draining Decoction (三黃瀉心湯 sān huáng xiè xīn tāng), Six-Ingredient Rehmannia Pill (六味地黃丸 liù wèi dì huáng wán), Ginkgo (銀杏 yín xìng; the nuts of *Ginkgo biloba*), Ganoderma (靈芝 líng zhī; *Ganoderma lucidum*) and Curcumae Longae Rhizoma (薑黃 jiāng huáng), are farther discussed in detail.

To understand the number and the objectives of papers utilizing DNA microarray for herbal medicine study, we surveyed 297 frequently used Chinese medicinal herbs listed in Pharmacopoeia Commission of People's Republic of China. We classified these medicinal herbs into 109 families and then applied PudMed search using "microarray" and individual herbal family as keywords. We found that microarray technology has been utilized in studying 62 herbal families and 2,674 articles applying microarray technology in the studies of these herbal families have been published in the years 1998 to 2011. The top ten herbal families applying microarray analysis are *Cruciferae* (974 articles), *Gramineae* (550 articles), *Suidae* (325 articles), *Fabaceae* (206 articles), *Solanaceae* (206 articles), *Compositae* (43 articles), *Vitaceae* (42 articles), *Rosaceae* (38 articles), *Malvaceae* (36 articles), and *Rutaceae* (35 articles). Moreover, the number of papers is increasing year by year (Figure 1).

We further analyzed the objectives of articles applying microarray for the studies of herbal families. Most of the articles use plant microarray to investigate

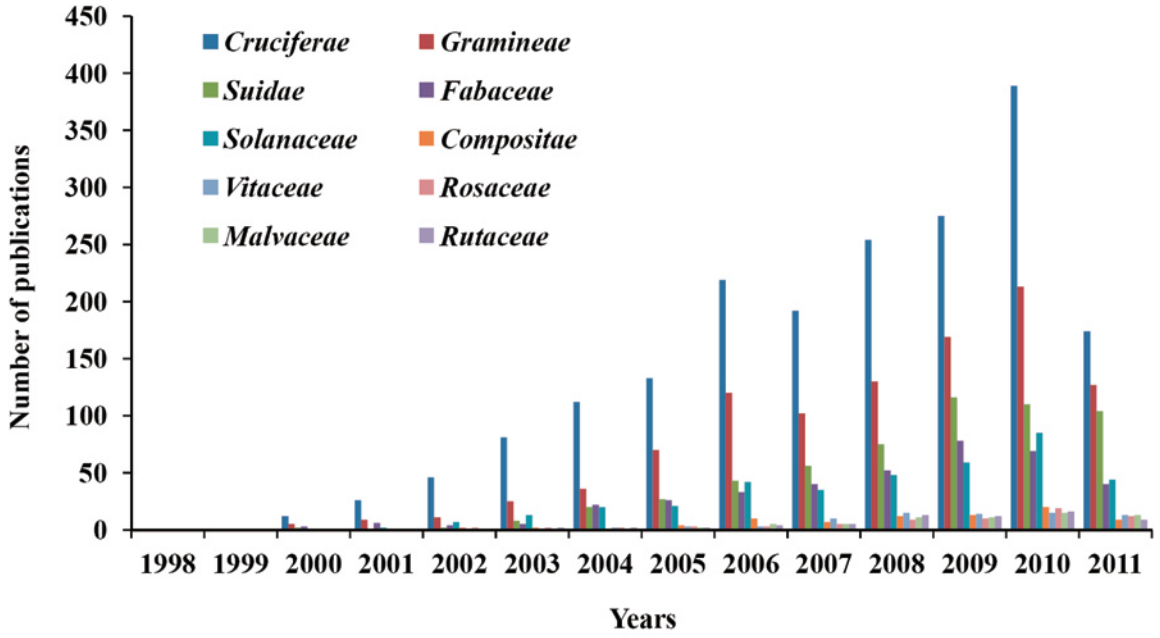

Figure 1. Number of publications of ten taxonomic families in the years 1998 to 2011. Bibliographic search using "microarray" and individual herbal taxonomic family as keywords was performed in January 2012.

the physiology, metabolism, or reproduction of herbs (O'Rourke et al., 2009). For examples, plant microarray has been utilized to elucidate the genes involved in flower development and to identify the key regulator of floral initiation (Kaufmann et al., 2010; Wellmer et al., 2006). It has also been employed to analyze the chloroplast processes of plants (Kleine and Leister, 2011). Moreover, because the genome-wide expression profiling is the output of the whole genomic regulatory patterns, it can provide a starting point for understanding the regulatory mechanisms of different developmental stages, cell types, and environmental conditions (Forment et al., 2005; Orlando et al., 2009). DNA microarray spotted with oligonucleotides matched to the nuclear 18S rRNA gene has been developed for authentication of ginseng (Zhu et al., 2008). After hybridization under optimal condition, specific fluorescent patterns can be detected for different *Panax* species. These findings suggested that DNA microarray designed to distinguish the polymorphisms of medicinal herbs can provide a reliable and objective method to authenticate the species, origins, culture conditions, and quality control of medicinal herbs (Wang et al., 2009; Zhang et al., 2007).

In addition to herbal physiology, microarray technology has been used to evaluate the host/herb interaction and to characterize the biological activities and mechanisms of herbal formulae and herbal compounds. For examples, Three Yellows Heart-Draining Decoction (三黃瀉心湯 sān huáng xiè xīn tāng), also named as San-Huang-Xie-Xin-Tang (SHXXT), has been used for the treatment of liver diseases. Microarray analysis indicates that SHXXT and its components display a unique anti-proliferation activity via p53 and DNA damage signaling pathways in HepG2 cells (Cheng et al., 2008). PC-SPES is a dietary supplement that has been used as an alternative therapy in patients with prostate carcinoma (Kubota et al., 2000; Small et al., 2000). The gene expression profile in cultured cells that have been exposed to PC-SPES shows that differential expression of genes involved in modulating cell cycle, cell structure, and androgen response may contribute to the PC-SPES-mediated cytotoxicity (Olaku and White, 2011). Six-Ingredient Rehmannia Pill (六味地黃丸 liù wèi dì huáng wán), as named as Yukmijihwang-tang (YMJ), has been widely used as an anti-aging herbal formula in Asian countries (Bonham et al., 2002). Microarray data indicate that YMJ enhances memory retention by inducing several genes that are involved in protecting neuronal cells, enhancing cell proliferation, and stimulating neurite growth (Hsieh et al., 2003). In addition, Danshen (the roots of *Salvia miltiorrhiza*)-Gegen (the roots of *Pueraria lobata*) Decoction (黨參葛根湯 dǎng shēn gé gēn tāng) has been used for the treatment of cardiovascular diseases (Worldwide clinical trial listing, 2008). Microarray data show that Danshen-Gegen decoction stimulates the proliferation of myocardium

cells via mitogen-activated protein kinase and insulin signaling pathways (Fong et al., 2011). These articles indicate that microarray can be applied to elucidate the therapeutic mechanisms of Chinese medicinal herbs with multiplex constitutes.

We further surveyed the articles applying microarray to study 297 frequently used Chinese medicinal herbs. Microarray technology has been employed in studying 50 medicinal herbs and 405 articles have been published from 1998 to 2011 (Table 1). Most of the articles focus

Table 1. List of Chinese medicinal herbs and herbal compounds that have been analyzed by microarray technology.

Family[a]	Latin name (pinyin) [b]	Compound[b]
Acanthaceae (2)	*Baphicacanthus cusib* (qīng dài) (0) [c]	Indigotin (2)
Anacardiaceae (6)	*Melaphis chinensis* (wǔ bèi zǐ) (0)	Gallic acid (6)
Araceae (3)	*Pinellia ternata* (bàn xià) (3)	Homogentisic acid (0)
Araliaceae (35)	*Panax ginseng* (rén shēn) (16)	Ginsenoside (12)
	Panax notoginseng (sān qī) (2)	Notoginsenoside (0)
	Periploca sepium (wǔ jiā pí) (0)	Sesamin (5)
Arecaceae (48)	*Areca catechu* (dà fù pí) (10)	Catechin (38)
Aristolochiaceae (13)	*Aristolochia debilis* (mǎ dōu líng) (3)	Magnoflorin (0)
	Aristolochia fangchi (guǎng fáng jǐ) (0)	Aristolochic acid (10)
	Aristolochia manshuriensis (guān mù tōng) (0)	Aristolochic acid (10)
Berberidaceae (1)	*Epimedium brevicornum* (yín yáng huò) (0)	Icariin (1)
Bignoniaceae (14)	*Campsis grandiflora* (líng xiāo huā) (0)	Apigenin (10)
	Oroxylum indicum (mù hú dié) (0)	Baicalein (4)
Bombycidae (1)	*Bombyx batryticatus* (bái jiāng cán) (0)	3-Hydroxy kynurenine (1)
Boraginaceae (3)	*Arnebia euchroma* (zǐ cǎo) (0)	Shikonin (3)
Bovidae (22)	*Calculus bovis* (niú huáng) (0)	Bilirubin (22)
Burseraceae (11)	*Commiphora myrrha* (mò yào) (0)	Eugenol (7)
	Boswellia carteri (rǔ xiāng) (1)	Boswellic acid (3)
Caryophyllaceae (44)	*Dianthus superbus* (qú mài) (0)	Anthocyanin (44)
Combretaceae (1)	*Quisqualis indica* (shǐ jūn zǐ) (1)	Quisqualic acid (0)
Compositae (9)	*Artemisia annua* (qīng hāo) (3)	Qinghaosu (3)
	Artemisia argyi (ài yè) (0)	Sesquiterpenoids (2)
	Carthamus tinctorius (hóng huā) (1)	
Cruciferae (4)	*Isatis indigotica* (bǎn lán gēn) (0)	Indigotin (2)
	Rhaphanus sativus (lái fú zǐ) (0)	Sinapine (1)
	Sinapis alba (bái jiè zǐ) (1)	Sinigrim (0)
Cucurbitaceae (13)	*Benincasa hispida* (dōng guā zǐ) (0)	Citrulline (9)
	Trichosanthes kirilowii (guā lóu gēn) (4)	Campestol (0)
Cupressaceae (2)	*Platycladus orientalis* (cè bǎi yè) (2)	Thujene (0)
Cynomoriaceae (22)	*Cynomorium songaricum* (suǒ yáng) (0)	Saponin (22)
Caesalpiniaceae (1)	*Caesalpinia sappan* (sū mù) (1)	Barsilin (0)
Cannabidaceae (5)	*Cannabis sativa* (huǒ má rén) (5)	Trigonelline (0)
Ebenaceae (1)	*Diospyros kaki* (shì dì) (1)	Hydroxytriterpenic acid (0)
Equisetaceae (13)	*Equisetum hyemale* (mù zéi) (0)	Succinic acid (12)
	Euphorbia kansui (gān suì) (1)	Euphornin (0)
Eucommiaceae (1)	*Eucommia ulmoides* (dù zhòng) (1)	
Euphorbiaceae (29)	*Croton tiglium* (bā dòu) (3)	
	Euphorbia helioscopia (zé qī) (0)	Quercetin (26)
Fabaceae (94)	*Acacia catechu* (ér chá) (1)	Gambirdine (0)
	Astragalus membranaceus (huáng qí) (3)	Astragaloside (1)
	Astragalus complanatus (huáng qí) (1)	Complanatuside (0)
	Cassia obtusifolia (cǎo jué míng) (0)	Emodin (10)
	Dolichos lablab (biǎn dòu) (0)	Palmitic acid (15)
	Gleditsia sinensis (zào jiá) (0)	Curcumin (32)
	Glycine max (dà dòu) (7)	
	Glycyrrhiza uralensis (gān cǎo) (0)	Glycyrrhizin (4)
	Pueraria lobata (gé gēn) (0)	Daidzein (16)
	Sophora flavescens (kǔ shēn gēn) (2)	Matrine (1)
	Sophora tonkinensis (guǎng dòu gēn) (0)	Matrine (1)
Ginkgoaceae (8)	*Ginkgo biloba* (shān dòu gēn) (8)	Ginkgotoxin (0)
Gramineae (87)	*Coix lacryma* (yì yǐ) (1)	
	Triticum aestivum (fú xiǎo mài) (86)	Allantonin (0)
Haliotidae (1)	*Haliotis diversicolor* (shí jué míng) (1)	Conchiolin (0)
Hamamelidaceae (1)	*Liquidambar formosana* (lù lù tōng) (0)	28-Noroleanoic acid (1)
Hirudinidae (2)	*Whitmanian pigra* (shuǐ zhì) (0)	Hirudin (2)

Family[a]	Latin name (pinyin) [b]	Compound[b]
Hyocraceae (20)	*Cordyceps sinensis* (dōng chóng xià cǎo) (1)	Cordycepic acid (19)
Labiatae (27)	*Scutellaria baicalensis* (huáng qín) (5)	Baiaclin (0)
	Lycopus lucidus (zé lán) (0)	Volatile oil (5)
	Perilla frutescens (zǐ sū yè) (1)	
	Salvia miltiorrhiza (dān shēn) (10)	Tanshinone (6)
Laminariaceae (38)	*Laminaria japonica* (hǎi dài) (0)	Alginate (38)
Lauraceae (5)	*Cinnamomum cassia* (ròu guì) (1)	Cinnamaldehyde (4)
Liliaceae (3)	*Anemarrhenae asphodeloides* () (1)	Timosaponin (0)
	Simlax glabra (tǔ fú líng) (2)	Astilbin (0)
Loranthaceae (26)	*Taxillus chinensis* (sāng jì shēng) (0)	Quercetin (26)
Magnoliaceae (15)	*Magnolia biondii* (xīn yí) (0)	β-Pinene (1)
	Magnolia officinalis (hòu pò) (14)	Magnolol (0)
Myrtaceae (7)	*Eugenia caryophyllata* (dīng xiāng) (0)	Eugenol (7)
Orchidaceae (1)	*Anoectochilus formosanus* () (1)	
Piperacea (3)	*Piper nigrum* (hú jiāo) (2)	Piperine (1)
Polygalaceae (1)	*Polygala tenuifolia* (yuǎn zhì) (1)	Tenuigenin (0)
Polygonaceae (14)	*Rheum officinale* (dà huáng) (4)	Emodin (10)
Polyporaceae (9)	*Ganoderma lucidum* (líng zhī) (8)	
	Polyporus umbellatus (zhū líng) (1)	Polyporusterone (0)
Punicaceae (18)	*Punica granatum* (shí liú pí) (0)	Tannin (18)
Ranunculaceae (29)	*Paeonia suffruticosa* (mǔ dān pí) (0)	Paeoniflorin (2)
	Aconitum carmichaeli (wū tóu) (0)	Aconitine (1)
	Anemone altaica (jiǔ jié chāng pú) (0)	Palmitic acid (15)
	Coptis chinensis (huáng lián) (1)	Berberine (10)
Rosaceae (113)	*Agrimonia pilosa* (xiān hè cǎo) (0)	Leuteolin-7-glucoside (13)
	Armeniaca vulgaris (kǔ xìng rén) (16)	Amygdalin (1)
	Chaenomeles speciosa (mù guā) (0)	Malic acid (5)
	Eriobotrya japonica (pí pá yè) (0)	Epicatechin (39)
	Photinia serrulata (shí nán) (0)	Nerolidol (2)
	Prunus armeniaca (xìng rén) (16)	Amygdalin (1)
	Prunus humilis (yù lǐ rén) (0)	Amygdalin (1)
	Prunus persica (táo rén) (16)	Amygdalin (1)
	Rubus chingii (fù pén zǐ) (0)	Ellagic acid (2)
Rubiaceae (15)	*Rubia cordifolia* (qiàn cǎo gēn) (0)	Alizarin (15)
Rutaceae (78)	*Citrus aurantium* (zhǐ qiào (ké)) (57)	Hesperidin (0)
	Dictamnus dasycarpus (bái xiān pí) (0)	Psoralen (5)
	Phellodendron amurense (huáng bǎi) (0)	Berberine (10)
	Poncirus trifoliata (zhǐ shí) (2)	Hesperidin (0)
	Zanthoxylum bungeanum (huā jiāo) (0)	Cinnamaldehyde (4)
Sargassaceae (18)	*Sargassum pallidum* (hǎi zǎo) (0)	Alginic acid (18)
Schizaeaceae (2)	*Lygodium japonicum* (hǎi jīn shā) (0)	Methylester (2)
Scrophlariaceae (24)	*Scrophullaria ningpoensis* (xuán shēn) (0)	Harpagide (1)
	Siphonlostegia chinensis (liú jì nú) (10)	Coumarin (13)
Solanaceae (26)	*Lycium barbarum* (gǒu qǐ) (0)	Betaine (26)
Sparganiaceae (5)	*Sparganium stoloniferum* (jīng sān léng) (0)	Benzeneethanol (5)
Suidae (51)	Suis Vesica Fellea (zhū dǎn) (51)	
Thymelaeaceae (1)	*Daphne genkwa* (yuán huā) (0)	Genkwanin (1)
Trogopterus (70)	*Trogopterus xanthipes* (wǔ líng zhī) (0)	Catechol (70)
Typhaceae (7)	*Typha angustifolia* (xiāng pú) (0)	Naringenin (7)
Umbelliferae (4)	*Angelica dahurica* (bái zhǐ) (0)	Sitosterol (1)
	Angelica sinensis (dāng guī) (0)	Butylidenephthalide (1)
	Ligusticum sinense (gǎo běn) (0)	Limonene (1)
	Notopterygium incisum (qiāng huó) (0)	1,8-Cineole (1)
Violaceae (15)	*Viola philippica* (zǐ huā dì dīng) (0)	Palmitic acid (15)
Zingiberaceae (34)	*Alpinia oxyphylla* (yì zhì rén) (0)	1,8-Cineole (1)
	Amomum cardamomum (bái dòu kòu) (0)	1,8-Cineole (1)
	Curcuma longa (jiāng huáng) (12)	Turmerone (0)
	Curcuma wenyujin (yù jīn) (0)	Curcumin (32)
	Kaempferia galanga (shān nài) (0)	Kaempferol (9)
	Alpinia officinarum (gāo liáng jiāng) (0)	Curcumin (32)
Zygophyllaceae (9)	*Tribulus terrestris* (jí lí) (0)	Kaempferol (9)

[a] The number of publication enclosed in the parentheses is the sum of articles regarding herbs and compounds.
[b] The number of publications from 1998 to 2011 is enclosed in the parentheses.
[c] Because some publications analyze compounds but not plants, there is no publication for plants.

on the elucidation of mechanisms of medicinal herbs, while others discover novel therapeutic potentials of herbs. For examples, ginkgo (銀杏 yín xìng; the nuts of *Ginkgo biloba*) leaf extract EGb 761 is widely used in patients with neurodisorders, and it is the top-selling herbal drug in the world (Mahadevan and Park, 2008). Gene expression profiling of brains of mice given with EGb761 shows that EGb761 affects neuroactive ligand-receptor interaction pathway and up-regulates the subgroup of dopamine receptors, especially dopamine receptor 1a. *Ginkgo biloba* increases the expression of dopamine receptor 1 in brain, may explain why EGb761 can be used to treat neurodisorders (Su et al., 2009). In addition to the well-known efficacy of EGb761 in neurodisorders, novel therapeutic potentials of EGb761 can be predicted by microarray analysis. Bidon et al. (2009) found that EGb 761 induces a gain in muscular mass that is associated with an improvement of the muscular performances. DNA microarray shows that these modifications are contributed by genes related to myogenesis via transforming growth factor-β signaling pathway and to energy production via fatty acids and glucose oxidation. Their findings suggest that EGb 761 may be a novel treatment for sarcopenia. Ganoderma (靈芝 líng zhī; *Ganoderma lucidum*) is a well-known immunomodulatory herb (Xu et al., 2011). Immunization of polysaccharide from *Ganoderma lucidum* (PS-G) increases IgG2a levels in mice, suggesting that PS-G effectively promotes the activation and maturation of immature dendritic cells, preferring a T helper 1 response. Microarray data of dendritic cells exposed to PS-G show that genes associated with phagocytosis are decreased and genes associated with proinflammatory chemokines and cytokines are increased. Their results also demonstrate that the microarray data are correlated with the *in vivo* effect of the immune-enhancing compound PS-G (Lin et al., 2006). Pinelliae Rhizoma (半夏 bàn xià; the roots of *Pinellia ternate*) extract (PRe) has been used to treat cough, asthma, and psychological diseases (Kang et al., 2005). Microarray analysis of mice exposed to psychological stress shows that the expression of genes that are altered in response to psychological stress is restored to normal levels in PRe-treated mice (Kim et al., 2010). Araliae Cordatae Rhizoma et Radix (當歸 dāng guī; the roots of *Angelica sinensis*) has been widely used in skin and wound care (Majewska and Gendaszewska-Darmach, 2011). An aqueous isolate (SBD.4) of *Angelica sinensis* increases the strength of healed wounds in older rats. Microarray analysis of SBD.4 in zebrafish angiogenesis model and human skin substitutes further reveals a bioactivity profile consistent with skin repair and regeneration (Zhao et al., 2011).

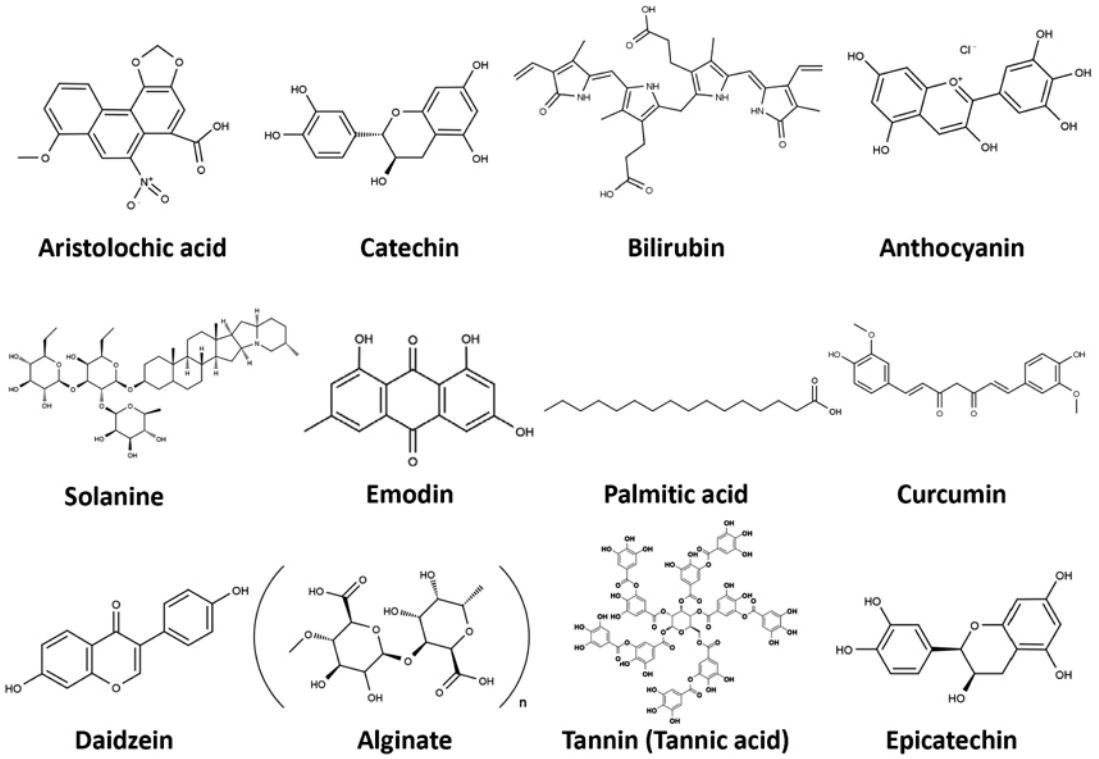

Figure 2. Chemical structures of representative herbal compounds.

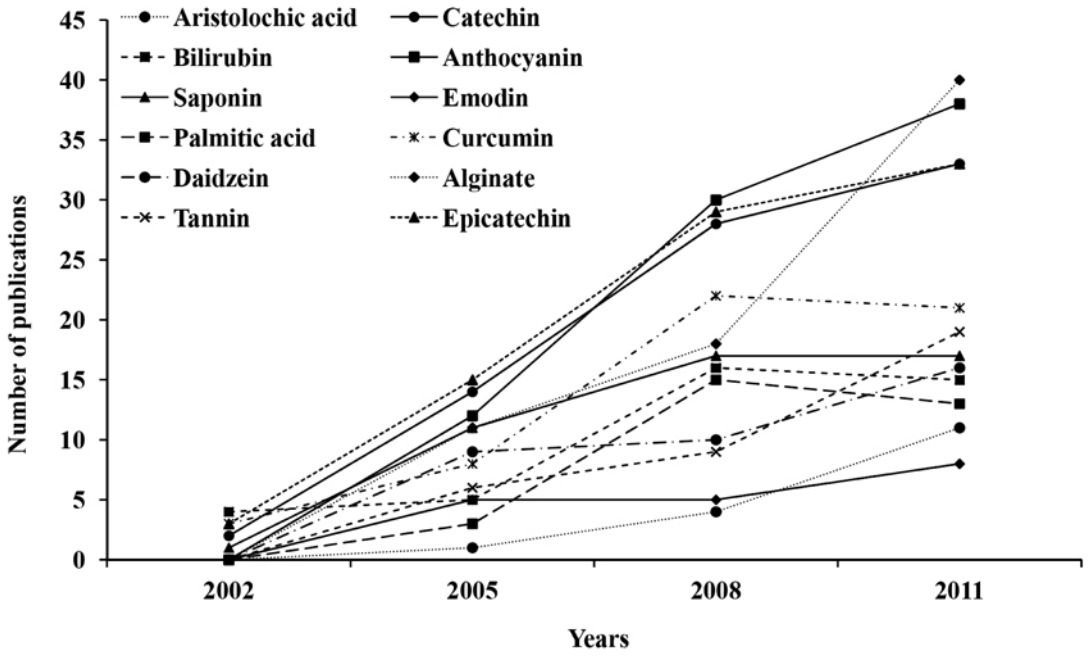

Figure 3. Number of publications of representative herbal compounds in the years 1998 to 2011. Bibliographic search using "microarray" and individual herbal compound as keywords was performed in January 2012. Data are the sum of articles within three years.

In addition to Chinese medicinal herbs, we also surveyed the number and objectives of articles applying microarray analysis to study herbal compounds. The structures of representative compounds are shown in Figure 2. A total of 1,196 articles has been published from 2000 to 2011, and the number of papers is increasing year by year (Figure 3). Most of the articles aim to elucidate the mechanisms of herbal compounds, while others predict the novel therapeutic potentials or toxicological effects of compounds. For examples, curcumin is a major chemical component of Curcumae Longae Rhizoma (薑黃 jiāng huáng; the roots of *Curcuma longa*) , which has been used as a spice to give a specific flavor and yellow color to curry (Govindarajan, 1980). Curcumin displays anti-carcinogenic properties in animals (Huang et al., 1988). Microarray analysis indicates that curcumin exhibits a novel anti-metastatic effect via regulating the expression of certain genes involved in metastasis (Chen et al., 2004). Aristolochic acid (AA), the major constitute of *Aristolochia* species, is a carcinogenic and nephrotoxic chemical (Lai et al., 2009). Microarray analysis shows that most AA-altered genes are connected with nuclear factor-κB (NF-κB), suggesting that NF-κB plays a critical role in the pathogenesis of AA-induced renal diseases (Chen et al., 2010). Emodin, the active principle of herbal medicine derived from genera *Rheum* and *Polygonum*, is a well-known inhibitor of casein kinase II (CK2) (Yim et al., 1999). Microarray analysis of mice testis exposed to emodin shows that emodin causes testicular toxicity via apoptosis through insulin-like growth factor-1 receptor signaling pathway and affects CK2, spermatogenesis, and sperm motility via four pathways, such as tumor necrosis factor receptor 1 signaling (Oshida et al., 2011). Silymarin, a flavonoligan mixture of milk thistle (*Silybum marianum*), is a well-known hepatoprotective drug (Abenavoli et al., 2010). Microarray analysis of carbon tetrachloride-treated livers in mice shows that silymarin alters the transforming growth factor-β-mediated pathways and downregulates the expression levels of cytoskeleton organization genes and mitochondrion electron-transfer chain genes, such as cytochrome *c* oxidase Cox6a2, Cox7a1, and Cox8b genes (Li et al., 2012). By investigating the herbal compounds that have employed microarray analysis, we found that most of the articles aim to elucidate the mechanisms of herbal compounds and to predict the novel therapeutic potential or toxicological effects of compounds (Cheng et al., 2007; Cheng et al., 2009; Leow et al., 2011). Therefore, construction of databases containing all the published gene expression profiles of herbs may provide the basis for the comparison between herbal compounds and drugs, and for the study of drug/gene interaction.

Conclusion

Although thousands of papers applying DNA microarray for Chinese herbal study have been published since 1998, most of the articles focus on the elucidation of mechanisms of certain biological effects of herbs. DNA microarray is a high-throughput platform that enables researchers to monitor the expression of thousands of genes simultaneously. The linkage between gene expression signatures can be a powerful tool for the comparisons of drugs with or without defined mechanisms. Therefore, a large-scaled genome-wide expression profiling can provide a comprehensively and globally view for the mechanisms, biological activities, therapeutic potential, and toxicology of drugs (Chang et al., 2011; Chang et al., 2012; Fernandes et al., 2009; Gidrol et al., 2009; Lu et al., 2012; Ulrich-Merzenich et al., 2010). For examples, the large-scaled gene expression analysis of toxin-treated cells and animals has been utilized to recognize the toxic potentials of novel drug candidates (Ganter et al., 2005). The large-scaled gene expression profile can be used to identify the disease target for drug development (Whitfield et al., 2006). Moreover, the therapeutic efficacy can be predicted *in vitro* on the basis of gene expression signatures (Gunther et al., 2003). Extracts prepared from medicinal plants contain various molecules with potent biological activities. However, it is difficult to analyze the biological activities of these extracts because of their complex constituents. To overcome this issue, we link the formulae-altered genes with drugs- or compounds-regulated genes by Connectivity Map (Cheng et al., 2010). Connectivity Map compares lists of differential expressed genes to a library of experiments evaluating the effects of small molecules and genetic events on gene expression (Lamb et al., 2006; Lamb, 2007). Connectivity Map searches for connections among molecules sharing similar mechanisms of action. By connecting the gene expression signatures of formulae with those of drugs, we can anticipate the novel therapeutic potential of herbs and further identify the phytochemical candidate for drug development. In the future, construction of the bioactivity database containing large-scaled gene expression profiles of quality control herbs can be applied to analyze the biological events induced by herbs, to predict the therapeutic potential of herbs, to evaluate the safety of herbs, and to identify the drug candidate of herbs. In addition, such a database can be served as a translational platform between traditional Chinese herbal medicine and Western medicine.

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