Abstract: The application of DNA microarray assay (DMA) has entered a new era owing to recent innovations in omics technologies. This review summarizes recent applications of DMA-based gene expression profiling by focusing on the screening and characterization of traditional Chinese medicine. First, herbs, mushrooms, and dietary plants analyzed by DMA along with their effective components and their biological/physiological effects are summarized and discussed by examining their comprehensive list and a list of representative effective chemicals. Second, the mechanisms of action of traditional Chinese medicine are summarized by examining the genes and pathways responsible for the action, the cell functions involved in the action, and the activities found by DMA (silent estrogens). Third, applications of DNA for traditional Chinese medicine are discussed by examining reported examples and new protocols for its use in quality control. Further innovations in the signaling pathway-based evaluation of beneficial effects and the assessment of potential risks of traditional Chinese medicine are expected, just as are observed in other closely related fields, such as the therapeutic, environmental, nutritional, and pharmacological fields.

Keywords: DNA microarray; traditional Chinese medicine; signaling pathway; estrogen; food chemicals

1. Introduction

Herbal medicine is an important part of the medical practices in traditional Chinese medicine (TCM), and consists of a variety of plant species [1,2]. While the effectiveness of herbal medicine has sometimes been considered doubtful [3,4], this could be due in part to the difficulty of controlling the quality of herbs and the amounts of their effective components. Thus, various methods have been used to confirm their efficacy and identify the effective components [5]. Modern technologies, such as high-performance liquid chromatography (HPLC) and quantitative reverse-transcription polymerase chain reaction (qRT-PCR), have been continually developed and utilized to replace conventional technologies for the comprehensive and cost-effective quality control of herbal medicine [6]. Although recent progress in the human and other genome projects and the development of a variety of omics technologies—such as genomics and transcriptomics—have contributed to the identification and utilization of effective components and quality control/authentication of medicinal plants [7–11], we are still searching for the best strategy for the maximum utilization of herbal medicine. This review focuses on DNA microarray-based gene expression profiling, a key technology in transcriptomics, and shows how researchers used this technology for the screening and characterization of TCM. In particular, cross-examination of the data on TCMs, and their constituent herbs, mushrooms, and dietary plants, has become quite important to evaluate the knowledge accumulated and to assess the advantages/disadvantages of TCM and its effective applications.

TCM includes practices such as acupuncture, moxibustion, Chinese herbal medicine, tui na, dietary therapy, tai chi, and qi gong, which is rooted in the ancient philosophy of Taoism and is more
than 2500 years old [12]. The original TCM has been further developed and modified to adapt it to people of various nationalities and genetic backgrounds (giving rise to different types of health problems, dietary and nutritional customs/practices, and ways of thinking and beliefs about medicine), based on variations in the types of herbs and their ingredients in countries such as Japan and Korea, where Kampo and traditional Korean medicine (TKM), respectively, were developed. Therefore, herbal medicine includes a number of plant species and ways of processing them. Furthermore, herbal medicine is often used with other constituents such as mushrooms and dietary plants, and thus their extracts and effective chemicals are also discussed here.

DNA microarrays are a type of biotechnological device used to detect alterations in genomic DNA and mRNA and to monitor genes and their expressions associated with various functions; thus, they have been widely used in basic research and industrial research/development (reviewed by Kiyama & Zhu [13]). DNA microarray assay (DMA) has been used to screen and characterize useful materials among mixtures of chemicals and extracts of natural resources including plants. DMA has advantages and disadvantages compared with other technologies. It has been used as a diagnostic device, such as for the genotyping of drug-metabolizing genes and predicting the metastatic risk of breast cancer, which is attributable to its unique characteristic of providing sufficient complexity to differentiate the variations needed for diagnosis and the reliability needed to predict genotypes/gene expression profiles accurately.

2. Herbal Medicine, Effective Chemicals, and Their Effects

2.1. Herbs, Mushrooms, and Dietary Plants Analyzed by DNA Microarray Assays

A number of herbs, mushrooms, and dietary plants, including those used as TCM in China, Korea (TKM), and Japan (Kampo), have been analyzed by DMA (Table 1).

Table 1. Herbs, traditional medicines, mushrooms, and dietary plants analyzed by DNA microarray assay (DMA).

| Herb                              | Extract or Material Examined | Pathway or Function Examined/Identified | Reference (Assay *) |
|-----------------------------------|------------------------------|----------------------------------------|---------------------|
| Actaea racemosa (Black cohosh)    | Extract                      | Anti-carcinogenesis                    | Einbond et al., 2012 [14] (A, C, T) |
| Angelica sinensis (Dong quai)     | Extract                      | Wound healing                          | Zhao et al., 2012 [15] (C, T) |
| Anoectochilus formosanus (an orchid) | Extract                      | Anti-carcinogenesis                    | Yang et al., 2004 [16] (C, T) |
| Astragalus propinquus,             | Radix extract                | Wnt signaling/Angiogenesis             | Zhang et al., 2011 [17] (C, P, T) |
|     Rehmannia glutinosa Radix      |                              |                                        |                     |
| Boswellia serrata (Salai)         | Extract                      | Anti-inflammation                      | Kiela et al., 2005 [18] (A, C, R, T) |
| Chelidonium majus (Greater celandine) | Extract (Alkaloids)          | Anti-carcinogenesis                    | El-Readi et al., 2013 [19] (C, T) |
| Cistanche tubulosa                | Root extract                 | Anti-atherosclerosis                    | Shimoda et al., 2009 [21] (A, T) |
| Coptis chinensis (Chinese goldthread) | Rhizome extract              | p53 signaling                          | Cheng et al., 2008 [22] (C, T) |
| Coptis japonica (Goldthread)      | Rhizome extract              | Anti-carcinogenesis                    | Iizuka et al., 2003 [23] (C, T) |
| Coptis japonica (Goldthread)      | Rhizome extract              | Anti-carcinogenesis                    | Kang et al., 2005 [24] (C, P, T) |
| Curcuma longa (Turmeric)          | Extract                      | Anti-inflammation                      | Kim et al., 2013 [25] (A, C, T) |
| Curcuma longa (Turmeric)          | Essential oil                | Anti-diabetic effect                   | Honda et al., 2006 [26] (A, T) |
| Dioscorea villosa (Wild yam),     | Extract                      | Anti-mitotic effect                    | Mazzio et al., 2014 [27] (C, T) |
| Lithospermum canescens (Alkanet root), |                            |                                        |                     |
| Trillium erectum (Beth root)      | Extract                      | Anti-mitotic effect                    | Mazzio et al., 2014 [27] (C, T) |
| Echinacea purpurea (Purple coneflower) | Extract                      | Immune response                        | Wang et al., 2006 [28] (C, T) |
| Echinacea purpurea (Purple coneflower) | Extract                      | Immune response                        | Wang et al., 2008 [29] (C, P, T) |
| Equisetum arvense (Field horsetail) | Extract                      | Metabolism/Stress response             | Cook et al., 2013 [30] (C, T) |
| Eupatorium perfoliatum (Boneset)  | Extract                      | Anti-inflammation                      | Maas et al., 2011 [31] (C, P, T) |
Table 1. Cont.

| Source | Extract or Material Examined | Pathway or Function Examined/Identified | Reference (Assay #) |
|--------|-----------------------------|----------------------------------------|---------------------|
| Hedyotis diffusa | Extract | Anti-carcinogenesis | Kuo et al., 2015 [32] (C, T) |
| Hypericum perforatum (St. John’s wort) | Extract | Antidepressant | Wong et al., 2004 [33] (A, T) |
| Hypericum perforatum (St. John’s wort) | Extract | Neurological disease/Angiogenesis | McCue & Phang, 2008 [34] (A, P, T) |
| Levisticum officinale (Lovage) | Essential oil | Cell proliferation | Sertel et al., 2011 [35] (C, T) |
| Nelumbo nucifera (Lotus) | Seed extract | MAPK/NO/Anti-inflammation | Sohn et al., 2009 [36] (C, P, T) |
| Nelumbo nucifera (Lotus) | Seed extract | Neuroprotection | Lee et al., 2010 [37] (A, T) |
| Paeonia lactiflora (Chinese peony) | Root extract | Apoptosis | Lee et al., 2002 [38] (C, T) |
| Paeonia suffruticosa (Moutan) | Extract | Anti-inflammation | Yun et al., 2012 [39] (C, T) |
| Panax quinquefolius (American ginseng) | Extract | Anti-carcinogenesis | Luo et al., 2008 [40] (C, T) |
| Piper methysticum (Kava) | Extract | Hepatotoxicity | Guo et al., 2012 [41] (A, T) |
| Piper methysticum (Kava) | Extract | Hepatotoxicity | Guo et al., 2009 [42] (A, T) |
| Salvia miltiorrhiza, Pueraria lobata | Root extract | MAPK/Insulin signaling | Fong et al., 2011 [43] (C, P, T) |
| Scrophularia ningpoensis (Chinese figwort) | Extract | MAPK/NF-κB/Apoptosis | Shen et al., 2012 [44] (C, P, T) |
| Scleranthus barbatus (Barbed skullcap) | Extract | Anti-carcinogenesis | Yin et al., 2004 [45] (C, T) |
| Sutherlandia frutescens (Cancer bush) | Extract | Apoptosis | Standler et al., 2007 [46] (C, T) |
| Tabebuia avellanedae (Pink Lapacho) | Extract | Apoptosis | Mukherjee et al., 2009 [47] (C, T) |
| Tripterygium wilfordii (Leigongteng) | Extract | PPAR/Hepatotoxicity | Zhang et al., 2012 [48] (A, T) |
| Vitis rotundifolia (Beach vitex) | Extract | MAPK/Anti-inflammation | Sohn et al., 2009 [49] (C, T) |

**Mushroom**

| Agaricus bisporus (Common mushroom) | Extract | Anti-carcinogenesis | Adams et al., 2008 [50] (C, T) |
| Agaricus blazei (Hinematsutake) | Extract | Immune response | Ellertsen et al., 2006 [51] (P, T) |
| Agaricus blazei | Extract | Anti-carcinogenesis | Grinde et al., 2006 [52] (C, T) |
| Agaricus blazei | Mycelia extract | ERK/Anti-atherosclerosis | Dong et al., 2012 [53] (A, P, T) |
| Cordyceps sinensis (Caterpillar fungus) | Extract | TLR signaling | Li et al., 2012 [54] (C, T) |
| Daedalea gibbou (Lumpy bracket) | Extract | NF-kB/NO production | Ruimi et al., 2010 [55] (A, C, T) |
| Ganoderma lucidum (Lingzhi) | Extract (Polysaccharide-rich) | Apoptosis | Cheng et al., 2007 [56] (C, P, T) |
| Ganoderma lucidum | Extract | Anti-metastatic effect | Loganathan et al., 2014 [57] (A, C, T) |
| Ganoderma sinense (Lingzhi) | Extract | NF-κB/Anti-inflammation | Cheng et al., 2010 [58] (T) |
| Grifola frondosa (Maitake), Hypsizigus marmoreus (Buna-shimeji) | Extract | TLR3/IFN-β | Sato et al., 2011 [59] (A, T) |
| Lentinus edodes (Shiitake) | Mycelia extract | (Lignin-rich) Immune response | Kawano et al., 2010 [60] (C, P, T) |

**Mushroom blend (Agaricus blazei, Cordyceps sinensis, Coriolus versicolor, Ganoderma lucidum, Grifola frondosa, Polyporus umbellatus)**

| Mycelia extract | Anti-carcinogenesis | Jiang & Sliva, 2010 [61] (C, P, T) |

**Pleurotus ostreatus (Hiratake)**

| Extract | p53/Apoptosis | Jedinak & Sliva, 2008 [62] (C, P, T) |

**Pleurotus ostreatus (Hiratake), Ganoderma lucidum, Poria cocos (Hoelen)**

| Extract (Triterpene-rich) | Anti-carcinogenesis | Cheng et al., 2013 [63] (C, P, T) |

**Trametes versicolor (Turkey tail)**

| Extract | Apoptosis | Hsieh & Wu, 2006 [64] (C, P, T) |

**TCM/TKM/Kampo**

| Bosoito, Befutsushosan, Omeocolocto (Kampo) | Mixtures of herbs | Anti-adipogenesis | Yamakawa et al., 2008 [65] (C, T) |
| Changgan (TKM) | Mixture of 13 herbs | Anti-fibrotic effect | Kim et al., 2013 [66] (C, P, T) |
| Dansui Buxue Tang (TCM) | Mixture of two herbs | Proliferation/differentiation | Choi et al., 2011 [67] (C, P, P, T) |
| Guanxin No.2 decoction (TCM) | Mixture of five herbs | Cardioprotection | Zeng et al., 2009 [68] (A, T) |
| Hochu-ekki-to (Kampo) | Mixture of 10 herbs | Apoptosis | Tohda et al., 2008 [69] (C, T) |
| Hochu-ekki-to (Kampo) | Mixture of 10 herbs | Immune response | Matsumoto et al., 2010 [70] (A, P, T) |
Table 1. Cont.

| Source                                | Extract or Material Examined | Pathway or Function Examined/Identified | Reference (Assay *) |
|----------------------------------------|------------------------------|----------------------------------------|---------------------|
| Huang-Lian-Jie-Du decoction (TCM)      | Mixture of four herbs        | Alzheimer’s disease                     | Zheng et al., 2008 [72] (A, T) |
| Inchin-ko-to (Kampo)                   | Mixture of three herbs       | MAPK/Apoptosis                          | Sakaida et al., 2003 [73] (A, P, T) |
| ISF-1 (TCM)                            | Mixture of seven herbs       | Neuroprotection                         | Rong et al., 2007 [6] (C, T) |
| Juzen-taiho-to (Kampo)                 | Mixture of 10 herbs          | MAPK/Anti-carcinogenesis                | Zheng et al., 2014 [74] (A, T) |
| Juzen-taiho-to (Kampo)                 | Mixture of 10 herbs          | ISGF3-IRF7/IFα signaling                | Munakata et al., 2012 [75] (A, P, T) |
| Kangxianling (TCM)                     | Mixture five herbs           | TGFB1/Smad signaling                    | Dong et al., 2012 [76] (A, P, T) |
| Kossan (Kampo)                         | Mixture of five herbs        | Antidepressant                          | Hayasaki et al., 2007 [77] (C, T) |
| PC-SPES (TCM)                          | Mixture of eight herbs       | Anti-carcinogenesis                     | Bonham et al., 2002 [78] (C, T) |
| Pulstilla decoction (TCM)              | Mixture of four herbs        | Anti-endotoxin action                   | Hu et al., 2009 [79] (C, T) |
| Qingfei Xiaoyan Wan (TCM)              | Mixture of eight herbs       | Anti-inflammation/Anti-remodeling       | Zhao et al., 2013 [80] (A, P, T) |
| Qinggan Huoxxuefang (TCM)              | Mixture of five herbs        | Apoptosis                               | Ji et al., 2006 [81] (A, T) |
| Saireito (Kampo)                       | Mixture 12 herbs             | Immune response                         | Watanabe et al., 2010 [82] (A, T) |
| S/B remedy                             | Mixture of two herbs         | Cell proliferation                      | Wang et al., 2005 [83] (A, C, T) |
| SH21B (TKM)                            | Mixture of seven herbs       | Wnt signaling/Adipogenesis              | Lee et al., 2011 [84] (C, P, T) |
| Si-Wu-Tang (TCM)                       | Mixture of four herbs        | Chemoprevention                         | Wen et al., 2011 [85] (C, R, T) |
| Si-Wu-Tang (TCM)                       | Mixture of four herbs        | Gynecological diseases                  | Fang et al., 2013 [86] (C, T) |
| TCM                                    | Mixture of three herbs       | Estrogen/Anti-osteoporosis              | Sun et al., 2008 [87] (A, T) |
| TCM (15 formulae)                      | Mixtures of herbs            | Anti-carcinogenesis, etc.               | Cheng et al., 2010 [88] (A, T) |
| Toki-shakuyaku-san (Kampo)             | Mixture of six herbs         | Circulation disorders                   | Kawamura et al., 2007 [89] (C, T) |
| Toki-to (Kampo)                        | Mixture of 10 herbs          | Parkinson’s disease                     | Sakai et al., 2007 [90] (A, T) |
| VT-28 (TCM)                            | Mixture five herbs           | IGF-1/Immune response                   | Pan-Hammarström et al., 2006 [91] (C, T) |
| Xiaoqinglong decoction (TCM)           | Mixture of eight herbs       | Obstructive lung disease                | Zhang et al., 2012 [92] (A, T) |
| Xuefu Zhuyu decoction (TCM)             | Mixture of 11 herbs          | Angiogenesis modulation                 | Song et al., 2012 [93] (C, T) |
| Youkongdan (TKM)                       | Mixture 17 herbs             | Neuromodulation                         | Shin et al., 2004 [94] (A, T) |
| Zeng Sheng Ping (TCM)                  | Mixture of six herbs         | Chemoprevention                         | Zhang et al., 2004 [95] (A, T) |
| Dietary plant (Vegetable, Fruit, and Cereal) |                             |                                        |                     |
| Aframomum angustifolium                | Seed extract                 | Skin aging prevention                   | Bonnet-Duquennoy et al., 2007 [96] (C, T) |
| Allium sativum (Garlic)                | Extract                      | Caspase-3/Apoptosis                     | Su et al., 2006 [97] (C, P, T) |
| Allium sativum (Garlic)                | Extract                      | Anti-carcinogenesis                     | Frantz et al., 2000 [98] (C, T) |
| Apple                                  | Extract                      | NF-kB/Anti-inflammation                 | Jung et al., 2009 [99] (C, P, T) |
| Artemisia dracunculus (Tarragon)       | Extract                      | Insulin receptor signaling              | Wang et al., 2011 [100] (A, T) |
| Black raspberry                        | Extract                      | Anti-carcinogenesis                     | Wang et al., 2011 [101] (A, T) |
| Blueberry                              | Powder                       | Wnt signaling/Anti-carcinogenesis      | Adams et al., 2011 [102] (A, C, P, T) |
| Broccoli                               | Extract                      | TGF-β/Polyamine catabolism              | Furniss et al., 2008 [103] (C, P, T) |
| Camellia sinensis (Green tea)          | Extract                      | Lipid metabolism disorder               | Suzuki et al., 2013 [104] (A, T) |
| Ceratonia silique (Carob)              | Extract (Gallic acid-rich)   | Chemoprevention                         | Klenow et al., 2009 [105] (C, T) |
| Chungkookjang (Fermented soybean)      | Extract                      | TGF-β/Anti-inflammation                 | Hwang et al., 2011 [106] (C, T) |
| Citrus/Grape/Green tea                 | Extract                      | Leukocyte function                     | Salas et al., 2009 [107] (A, T) |
| Elaeis guineensis (Oil palm)           | Extract (Phenolics-rich)     | Anti-inflammation                       | Leow et al., 2013 [108] (A, T) |
| Fagopyrum esculentum (Buckwheat)       | Sprout extract               | Anti-inflammation                       | Ishii et al., 2008 [109] (A, C, P, T) |
| Ginkgo biloba (Ginkgo)                 | Extract                      | Neuromodulation                         | Watanabe et al., 2001 [110] (A, T) |
| Ginkgo biloba (Ginkgo)                 | Extract                      | Anti-carcinogenesis                     | Rimbach et al., 2003 [111] (T) |
| Grape                                  | Extract (Oleanolic acid-rich)| Anti-obesity                            | Yunoki et al., 2008 [112] (A, T) |
Table 1. Cont.

| Source                     | Extract or Material Examined | Pathway or Function Examined/Identified | Reference (Assay a) |
|----------------------------|-------------------------------|----------------------------------------|---------------------|
| Grape                      | Extract (Anthocyanin-rich)    | Anti-inflammation                      | Lefevre et al., 2008 [113] (A, T) |
| Grape                      | Seed extract (Proanthocyanidin-rich) | Cardioprotection                      | Bagchi et al., 2003 [114] (C, T) |
| Grapefruit                 | Extract                       | AhR/Chemoprevention                    | de Waad et al., 2008 [115] (C, R, T) |
| Green tea                  | Extract                       | Cytotoxicity                           | Yang et al., 2006 [116] (C, T) |
| Kiwifruit                  | Extract                       | Immune response                        | Edmunds et al., 2012 [117] (A, P, T) |
| Litchi chinensis (Lychee)  | Pericarp extract              | Estrogen/Anti-carcinogenesis           | Wang et al., 2006 [118] (C, P, T) |
| Lithospermum erythrorhizon (Gromwell) | Extract                        | Stress response                        | Bang et al., 2014 [119] (C, T) |
| Malus domestica (Marie Ménard apple) | Powder (Polyphenol-rich) | Anti-inflammation                      | Castagnini et al., 2009 [120] (A, T) |
| Momordica charantia (Bitter gourd) | Extract                       | TNF-α/Anti-inflammation                | Kobori et al., 2008 [121] (C, P, T) |
| Nectarine, Peach           | Extract                       | DNA damage prevention                  | Croteau et al., 2010 [122] (A, P, T) |
| Olive                      | Virgin olive oil              | Cardioprotection                       | Camargo et al., 2010 [123] (C, T) |
| Persimmon                  | Peel extract                  | Insulin signaling                      | Iizuchi et al., 2011 [124] (A, P, T) |
| Pistachio                  | Oil extract                   | Inflammatory response                  | Zhang et al., 2010 [125] (C, T) |
| Salacia reticulata (Kothala himbutu) | Extract                       | Inflammatory response                  | Im et al., 2008 [126] (A, T) |
| Soybean                    | Extract                       | Estrogen signaling                     | Ise et al., 2005 [127] (C, T) |
| Sweet corn                 | Powder                        | Wnt signaling/Anti-carcinogenesis      | Tokui et al., 2009 [128] (A, T) |
| Syzygium aromaticum (Clove) | Extract                       | Anti-diabetic                          | Prasad et al., 2005 [129] (C, T) |
| Toona sinensis (Chinese mahogany) | Leaf extract                 | Apoptosis                              | Chia et al., 2010 [130] (C, T) |
| Vaccinium myrtillus (Bilberry) | Powder                        | MAPK/Vision                            | Mykkänen et al., 2012 [131] (A, T) |

a Abbreviations for assays are: animal test (A), cell-proliferation assay (C), protein assay such as Western blotting and immunoblot assay (P), reporter gene assay (R) and transcription assay (such as RT-PCR and DNA microarray assay) (T). AhR: aryl hydrocarbon receptor; ERK: extracellular signal-regulated kinase; IF: interferon; IGF-1: insulin-like growth factor 1; IRF7: Interferon regulatory factor 7; ISGF3: Interferon-stimulated gene factor 3; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells; NO: nitric oxide; PPAR: peroxisome proliferator-activated receptor; TCM: traditional Chinese medicine; TGF: tumor growth factor; TKM: traditional Korean medicine; TLR: Toll-like receptor; TNF: tumor necrosis factor.

Extracts from herbs have been analyzed by DMA, including the following: extracts of the whole, or parts such as flower and leaves, of alkanet root, American ginseng, barbed skullcap, beach vitez, beth root, black cohosh, cancer bush, Chinese figwort, boneset, dong quai, field horsetail, greater celandine, kava, leigongteng, moutan, mum, orchid, pink lapacho, purple coneflower, salai, St. John’s wort, turmeric, and wild yam. Meanwhile, the extracts of root, radix or rhizome were made from Chinese goldthread, Chinese peony, cistanche, danshen, goldthread, huang-qì, kudzu, and sheng-di-huang; the extracts of seeds were from lotus; or the extracts enriched in essential oil were from lovage and turmeric.

The extracts from mushrooms were also analyzed after extraction of the whole or the fruiting body, such as that from buna-shimeji, caterpillar fungus, common mushroom, himematsutake, hiratake, lingzhi, lumpy bracket, maitake, and turkey tail; after extraction of the mycelium, such as that from caterpillar fungus, himematsutake, lingzhi, lumpy bracket, maitake, shiitake, and turkey tail; or after extraction of polysaccharides from lingzhi or triterpenes from hiratake, hoelen, and lingzhi.

Extracts were made from mixtures of TCM, such as the following: Danggui Buxue Tang, Guanxin No. 2 decoction, Huang-Lian-Jie-Du decoction, ISF-1, Kangxianling, PC-SPES, Pulsatilae decoction, Qingfei Xiaoyan Wan, Qinggan Huoxuefang, S/Sh remedy, Si-Wu-Tang, VI-28, Xiaoqinglong decoction, Xuefu Zhuyu decoction, and Zeng Sheng Ping (TCM); Chunggan, SH21B, and Youkongdan (TKM); or Boiogito, Bofutsushosan, Orenjedokuto, Hocchu-ekki-to, Inchin-ko-to, Juzen-taiho-to, Kososan, Saireito, Toki-shakuyaku-san, and Toki-to (Kampo).
Extracts were made from other dietary plants (including vegetables, fruit, and cereals), such as bilberry, bitter gourd, buckwheat, carob, Chinese mahogany, Chungkookjang (fermented soybean), ginger, gromwell, kothala himbutu, Marie Ménard apple, and tarragon, or more common food materials such as apple, black raspberry, blueberry, broccoli, citrus, clove, garlic, ginkgo, grape, grapefruit, green tea, kiwi fruit, lychee, nectarine, oil palm, olive, peach, persimmon, pistachio, soybean, and sweetcorn.

2.2. Effective Chemicals Characterized by DNA Microarray Assays

After characterization of the extracts of herbs, mushrooms, or dietary plants, effective chemicals have been enriched or, in some cases, purified. They were then analyzed by DMA in order to identify the functions of interest or the signaling pathways involved (Table 2).

| Chemical Examined (Category) | Major Source Examined/Identified | Pathway or Function | Reference (Assay *) |
|-----------------------------|----------------------------------|---------------------|---------------------|
| Actein (Terpenoid)          | Actaea racemosa (Black cohosh)   | Anti-carcinogenesis | Einbond et al., 2012 [14] (Table 1) |
| Aculeatin (Coumarin)         | Toddalia asiatica (Orange climber) | PPAR-γ/Adipogenesis | Watanabe et al., 2014 [132] (C, T) |
| Baicalin/Deoxycholic acid/Jasminoidin | Qing-Kai-Ling (TCM) | Ischemic stroke | Li et al., 2012 [133] (A, T) |
| Berberine (Alkaloid)         | Coptis japonica (Goldthread)     | Anti-carcinogenesis | Iizuka et al., 2003 [23] (Table 1) |
| Berberine, etc.              | Coptis japonica (Goldthread)     | Anti-carcinogenesis | Haru et al., 2005 [135] (T) |
| Biochanin A/Genistein (Flavonoid) | Plant (fruit/vegetables/leaves/grains) | Anti-carcinogenesis | Moon et al., 2007 [136] (C, T) |
| Boswellic acid (Terpenoid)   | Boswellia serrata (Salai)        | Chemoprevention     | Shen et al., 2012 [137] (C, T) |
| Brefeldin A (Lactone)        | Agaricus blazei                  | ERK/Anti-atherosclerosis | Dong et al., 2013 [138] (C, P, T) |
| Celastrol (Terpenoid)        | Tripterygium wilfordii (Leigongteng) | Anti-carcinogenesis | Pham et al., 2010 [139] (C, P, T) |
| Celastrol (Terpenoid)        | Celastrus scandens (Bittersweet) | Immune response     | Yu et al., 2012 [140] (T) |
| Chelidonine (Alkaloid)       | Chelidonium majus (Greater celandine) | Anti-carcinogenesis | El-Readi et al., 2013 [141] (Table 1) |
| Curcumin (Diarylheptanoid)   | Curcuma longa (Turmeric)         | Apoptosis           | Ramachandran et al., 2005 [142] (C, T) |
| Curcumin (Diarylheptanoid)   | Curcuma longa (Turmeric)         | Anti-oxidative response | Meja et al., 2008 [143] (C, T) |
| Curcumin (Diarylheptanoid)   | Curcuma longa (Turmeric)         | Life-span extension | Lee et al., 2010 [144] (T) |
| Diallyl trisulfide (Organosulfur) | Allium sativum (Garlic)         | skn-1/Life-span extension | Powolny et al., 2011 [145] (T) |
| 3,3'-Diindolylmethane         | Cruciferous vegetable            | Estrogen/Carcinogenesis | Tilton et al., 2007 [146] (A, T) |
| Emodin (Anthraquinone)       | Rheum palmatum (Turkish rhubarb) | TNFRI/IGF-1R/Apoptosis | Oshida et al., 2011 [147] (T) |
| Ergosterol peroxide (Steroid) | Sarcodion asperatus              | NF-κB/Anti-inflammatory | Kobori et al., 2007 [148] (C, P, T) |
| Ginsenosides F1/Rb1/Rg1/Rh1 (Terpenoid) | Ginseng | Estrogen signaling | Dong & Kiyama, 2009 [149] (T) |
| Ginsenoside Re (Terpenoid)   | Ginseng                          | Anti-diabetic response | Xie et al., 2005 [150] (T) |
| Ginkgolide I (Terpenoid)     | Panax quinquefolius (American ginseng) | Anti-carcinogenesis | Luo et al., 2008 [40] (Table 1) |
| Glycyrrhizin (Saponin)       | Glycyrrhiza glabra (Licorice)    | Estrogen signaling | Dong et al., 2007 [151] (T) |
| Glycyrrhizin (Saponin)       | Glycyrrhiza glabra (Licorice)    | Anti-inflammation | Schroflebauer et al., 2009 [152] (P, T) |
| Grape antioxidant dietary fiber | Cencibel red grape              | Anti-carcinogenesis | Lizzaraga et al., 2011 [153] (A, T) |
| Grifolin (Phenol)            | Albutellus confusus             | ERK/Anti-carcinogenesis | Ye et al., 2007 [154] (C, P, T) |
| Chemical Examined (Category) | Major Source Examined/Identified | Pathway or Function | Reference (Assay *) |
|-----------------------------|----------------------------------|--------------------|---------------------|
| (−)-Hydroxycitric acid      | *Garcinia gummi-gutta* (Garcinia cambogia) | Anti-obesity | Roy et al., 2007 [154] (T) |
| β-Hydroxyisovalerylshikonin (Quinone) | *Lithospermum erythrorhizon* (Purple gromwell) | ROS/Apoptosis | Masuda et al., 2004 [155] (C, P, T) |
| Ligustrazine (Tetramethylpyrazine) | *Ligusticum ehuanxing* | Cardioprotection | Li et al., 2004 [156] (T) |
| Lycopene (Carotenoid pigment) | Tomato | Stress response/ Anti-carcinogenesis | Tan et al., 2014 [157] (A, T) |
| Myricetin (Flavonoid) | Plant (fruits/vegetables/herbs) | Nrf2 /ARE/ Chemoprevention | Qin et al., 2013 [158] (T) |
| Obovatol (Phenol) | *Magnolia obvata* (Japanese bigleaf magnolia) | Neuroinflammation | Ock et al., 2010 [159] (A, C, P, T) |
| Oil palm phenolics | *Elaeis guineensis* (African oil palm) | Cardioprotection | Leow et al., 2011 [160] (A, T) |
| Paeoniflorin (Terpenoid) | *Paeonia lactiflora* (Chinese peony) | HSP70/Anti-carcinogenesis | Salunga et al., 2007 [161] (C, P, T) |
| Paeonol (Phenol) | *Paeonia suffruticosa* (Moutan) | NF-κB/Hypoxia | Su et al., 2010 [162] (P, R, T) |
| Paeonol/Paeoniflorin/Albiflorin | *Paeonia lactiflora* (Chinese peony) | Anti-inflammation | Huang et al., 2008 [163] (C, T) |
| PGG (Gallotannin) | *Rhus chinensis* (Sumac) | Anti-carcinogenesis | Yu et al., 2011 [164] (C, P, T) |
| Phytoester mixture | Wood (Tall oil) | Anti-atherosclerosis | Xu et al., 2008 [165] (A, T) |
| Plant phospholipid/lipid conjugate | Plant (nuts/seeds/oils) | Anti-carcinogenesis | Shuman Moss et al., 2014 [166] (A, T) |
| Plumbagin (Quinone) | *Anectochilus formosanus* (an orchid) | Anti-carcinogenesis | Yang et al., 2004 [16] (Table 1) |
| Polysaccharide-K (Krestin) | *Trametes versicolor* (Turkey tail) | Anti-carcinogenesis | Yoshikawa et al., 2004 [167] (C, T) |
| Polysaccharides | Apple | Anti-carcinogenesis | Li et al., 2012 [168] (C, P, T) |
| PUFA (n-3) | Corn, Olive | Anti-carcinogenesis | Kachroo et al., 2011 [169] (A, T) |
| PUFA's | *Camelina sativa* (False flax) | Cell proliferation | Morais et al., 2012 [170] (A, T) |
| Quercetin (Flavonoid) | Plant (fruits/vegetables/ leaves/grains) | NF-κB/Anti-carcinogenesis | Youn et al., 2013 [171] (C, P, T) |
| Resveratrol (Stilbenoid) | Red grape | Vasoprotection | Nicholson et al., 2008 [172] (Review) |
| Saffron | *Crocus sativus* (Saffron crocus) | Neuroprotection | Natoli et al., 2010 [173] (A, T) |
| Salvianolic acid B (Phenolic acid) | *Salvia miltiorrhiza* (Red sage) | Anti-carcinogenesis | Yang et al., 2011 [174] (C, P, T) |
| Sesamin/Episesamin/Sesamolin (Lignan) | Sesame | Lipid metabolism | Ide et al., 2009 [175] (A, T) |
| Spatholobin B (Isocoumarin) | *Sparganium stolonifera* (Bur-reed) | Angiogenesis | Bateman et al., 2013 [176] (C, T) |
| Sulforaphane (Organosulfur) | Broccoli | PI3K/Akt /Chemoprevention | Melchini et al., 2012 [177] (C, P, T) |
| 2,4,3′,5′-Tetramethoxystilbene (Stilbenoid) | Berry, Grape | Bax/Apoptosis | Aiyar et al., 2010 [178] (T) |
| Tanoshinone IIA (Quinone) | *Salvia miltiorrhiza* (Red sage) | Rho/ROCK/Cell migration | Li et al., 2014 [179] (C, P, T) |
| Tanoshinone IIA (Quinone) | *Salvia miltiorrhiza* (Red sage) | NF-κB/Apoptosis | Liu et al., 2012 [180] (C, P, T) |
| Triptolide (Terpenoid) | *Tripterygium wilfordii* (Leigongteng) | Immune response, etc. | Chen et al., 2007 [181] (A, T) |

* Abbreviations for assays are: animal test (A), cell-proliferation assay (C), protein assay (such as Western blotting and immunoassay) (P), reporter-gene assay (R) and transcription assay (such as RT-PCR and DNA microarray assay) (T). ARE: antioxidant response element; ERK: extracellular signal-regulated kinase; HSP70: 70 kilodalton heat shock protein; IF-IR: insulin-like growth factor 1 receptor; NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells; PGG: 1,2,3,4,6-Penta-O-galloyl-β-D-glucose; PI3K: phosphatidylinositol-3-kinase; PPAR: peroxisome proliferator-activated receptor; PUFA: polyunsaturated fatty acid; ROCK: Rho-associated protein kinase; ROS: reactive oxygen species; TCM: traditional Chinese medicine; TNFR1: tumor necrosis factor receptor 1.
Pure chemicals analyzed by DMA are as follows: actein (a triterpene glycoside), aculeatin (a coumarin), baicalin (a flavone glycoside), berberine (an isoquinoline alkaloid), biochanin A, boswellic acid (a triterpene), brefeldin A (a lactone antibiotic), celastrol (a quinine methide triterpene), chelidonine (a tertiary alkaloid), curcumin (a diarylheptanoid), deoxycholic acid (a steroid acid), 3,3′-diindolylmethane (an indole-3-carbinol derivative), emodin (an anthraquinone derivative), ergosterol peroxyde (a steroid derivative), genistein (an isoflavone), ginsenosides F1/Rb1/Re/Rg1/Rg3/Rh1 (steroid glycosides/triterpene saponins), glycyrrhizin (a pentacyclic triterpenoid), grifolin (a farnesylphenol/sesquiterpenoid), (−)-hydroxycitric acid (a derivative of citric acid), β-hydroxyisovalerylshikonin (a naphthoquinone derivative), jasminoidin (a geniposide), ligustrazine (a tetrapyrazine), lycopene (a carotene), myricetin (a flavonol), obovatol (a biphenolic), paeoniflorin (a monoterpene glycoside), paeonol (an acetophenone derivative), 1,2,3,4,6-penta-O-galloyl-β-D-glucose (PGG), plumbagin (a naphthoquinone derivative), polysaccharide-K (Krestin) (a protein-bound polysaccharide), resveratrol (a stilbenoid), salvianolic acid B (a tanshinol/caffeic acid), sesamin/episesamin/sesamolin (lignans), sialyl trisulfide (an organosulfur compound), sparstolonin B (a xanthone/isocoumarin), sulforaphane (an isothiocyanate), tanshinone IIA (a phenanthrene-quinone derivative), 2,4,3′,5′-tetramethoxystilbene (a phenylpropanoid), and triptolide (a diterpenoid epoxide).

On the other hand, mixtures of chemicals analyzed by DMA are: grape antioxidant dietary fiber (rougahage/dietary fiber), plant phospholipid/lipid conjugates, polysaccharides, and polyunsaturated fatty acids (PUFAs).

2.3. Biological/Physiological Effects Identified by DNA Microarray Assays

Biological/physiological effects and medicinal efficacy have been examined by DMA. To achieve this, a variety of assay systems have been used (Table 1), such as with different species (humans; animals, such as the chicken, dog, guinea pig, mouse, and rat; or microbes such as yeast and bacteria), tissues (brain, intestine, kidney, liver, lung, muscle, peripheral blood, or spleen) and cells (adenocarcinoma cells, alveolar epithelial cells, breast carcinoma cells, colon carcinoma cells, colorectal cancer cells, dendritic cells, dermal fibroblasts, endothelial cells, gingival fibroblasts, head and neck squamous cell carcinoma (HNSCC) cells, hepatoma cells, human umbilical vein endothelial cells (HUVECs), keratinocytes, lens tumor cells, leukemia cells, macrophages, neuroglial cells, oral squamous cell carcinoma cells, osteosarcoma cells, pancreatic cancer cells, peripheral blood mononuclear cells (PBMCs), preadipocytes, prostate cancer cells, rat intestinal microvascular endothelial cells (RIMECs), retinal cells, or skin fibroblasts); the assays examining the statuses in vitro (using cultured normal or cancer cells, or yeast or bacterial cells, such as A549, BxPc-3, Caco-2, colo 205, DU145, ECV304, H9c2, HaCaT, HepG2, HCT-116, HL-60, Hs27, HT-29, J774.1, LT97, MCF-7, MDA-MB-231, MG-63, MonoMac6, NG108-15, PC-3, RAW 264.7, THP-1, 3T3-L1, U1M1, UMSCC1, and YPK-1/4 cells) or in vivo (using tissues or cells from animals, or from healthy or diseased individuals); and DNA microarray platforms and assay protocols, such as those from ABIoscience, Affymetrix, Agilent Technologies, Applied Biosystems, Clontech, GE Healthcare, Illumina, Mitsubishi Rayon, SuperArray, and Takara, or customized ones (see Section 3).

The biological/physiological effects analyzed are as follows: the functions/effects examined are angiogenesis modulation, anti-adipogenesis, anti-atherosclerosis/anti-arteriosclerosis, antibiotic effect, anti-carcinogenesis/anti-metastasis, antidepressant effect, anti-diabetic/anti-obesity effect, anti-endotoxin action, anti-fibrotic effect, anti-inflammation/anti-remodeling, anti-mitotic effect, apoptosis, cardioprotection, cell proliferation/differentiation, chemoprevention, cytotoxicity, DNA damage prevention, hepatotoxicity, immune response, inflammatory response, leukocyte function, neuromodulation/neuroprotection, skin aging prevention, stress response, and wound healing. The assays revealed the receptor-related signaling, such as by aryl hydrocarbon receptor (AhR), insulin receptor, peroxisome proliferator-activated receptor (PPAR), and Toll-like receptor (TLR), or hormone/growth-factor-related signaling, such as estrogen signaling, IFα/IFβ signaling,
insulin-like growth factor 1 (IGF-1) signaling, and tumor necrosis factor α (TNF-α)/tumor growth factor β1 (TGF-β1) signaling, or signal-mediator-related signaling, such as caspase-3, extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), p53, and Wnt, or diseases/disorders, such as Alzheimer’s disease, circulation disorders, gynecological diseases, lipid metabolism disorders, obstructive lung disease, and Parkinson’s disease.

Meanwhile, the functions/effects identified by the analysis of pure chemicals (summarized in Table 2) are as follows: anti-carcinogenesis (actein, berberine, biochanin A, celastrol, chelidonine, genistein, ginsenoside Rg3, grape antioxidant dietary fiber, grifolin, lycopene, paoniflorin, PGG, plant phospholipid/lipid conjugate, plumbagin, polysaccharide-K (Krestin), polysaccharides, PUFAs, quercetin and salvianolic acid B); anti-atherosclerosis (brefeldin A and phytosterol mixture); anti-inflammation (ergosterol peroxide, glycyrrhizin, and paenol/paoniflorin/alfilin); immune response (celastrol, obovatol, and triptolide); anti-diabetic/anti-obesity response ((−)-hydroxycitric acid and ginsenoside Re); anti-infectious (berberine); apoptosis (curcumin, emodin, β-hydroxyisovalerylshikonin, tanshinone IIA, and 2,4,3′,5′-tetramethoxystilbene); anti-oxidative response (curcumin); adipogenesis/angiogenesis (acleutlein and spartolonolin B); cardio-, neuro-, or vasoprotection (ligustuzarina, oil palm phenolics, resveratrol, and saffron); cell proliferation (PUFAs); chemoprevention (boswellic acid, myricetin, and sulforaphan); estrogen signaling (3,3′-diindolylmethane, ginsenosides F1/ Rpc1/Rg1/Rh1, and glycyrrhizin); ischemic stroke (baicalin/deoxycholic acid/jasminoidin); hypoxia (paenol); life-span extension (curcumin and diallyl trisulphide); lipid metabolism (sesamin/episesamin/sesamolin); and Rho/ROCK (Rho-associated protein kinase) signaling (tanshinone IIA).

3. Mechanisms of Action by Traditional Chinese Medicine

DNA microarrays for gene expression analysis can be categorized into two types, global and focused DNA microarrays, based on their application [13,182]. Global DNA microarrays contain thousands to hundreds of thousands of probes representing some or all of the cDNA, expressed sequence tags (ESTs), and various types of expression marker, such as those for the estimation of mRNA copy numbers within cells. Meanwhile, focused DNA microarrays contain a few dozen to thousands of probes designed for specific purposes, such as the study of tissue/cell-type specificity, functional specificity, and expression profiling. Focused DNA microarrays are sometimes more appropriate for the study of the mechanisms of action when the action is known, such as in the case of comparative risk assessment of chemicals and the prediction of cancer metastatic risks.

The genes used in customized or focused DNA microarrays for basic research and the development of applications of TCM are as follows: sets of human apoptosis genes [38], 96 cancer-related genes [24], 225 genes related to chemotaxis/antigen processing/cell signaling/apoptosis/immune-related functions [28], mouse immunology-related genes [31], and 100 genes related to cardiac diseases, apoptosis, cell cycle/proliferation, cytokine/inflammatory, and antioxidation [43], for the study of herbs; genes related to growth factors/receptors, extracellular matrix components, proteases/inhibitors, and oncogenes/tumor suppressors [65], cell cycle-related genes [62,63], 172 human estrogen-responsive genes [53], and human pancreatic adenocarcinoma genes [64], for the study of mushrooms; sets of 3000 prostate-derived genes [78] and 1536 brain genes [72], for the study of TCM/TKM/Kampo; sets of 172 human estrogen-responsive genes [127], human drug metabolism-related genes [116], 209 inflammation/immune responsive genes [109], 2304 genes expressed in Caco-2 cells [115], 204 genes related to the immune response [121], and human apoptosis-related genes [130], for the study of dietary plants.

3.1. Genes and Pathways Responsible for the Action

The signaling pathways analyzed by DMA are as follows (see Kiyama & Zhu [13]; Kiyama et al. [183]): MAPK (such as G protein–coupled receptor (GPCR)/MAPK, MAPK/c-Jun
N-terminal kinase (JNK), and NF-κB/MAPK/ERK) and other (such as angiogenesis, ErbB/human epidermal growth factor receptor (HER), nuclear receptor, and ubiquitin/proteasome) signaling pathways, or apoptosis pathways (such as those for death receptor, infectious response, and p53-dependent apoptosis), autophagy pathways (such as those for phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR signaling and starvation stress response), cell cycle/DNA damage pathways (such as G1/S checkpoint and G2/M DNA damage checkpoint signaling pathways), cellular metabolism pathways (such as AMP-activated protein kinase (AMPK) and insulin receptor signaling pathways), chromatin/epigenetic regulation pathways (such as those for DNA methylation, heterochromatin, and histone modification), cytoskeletal regulation and adhesion pathways (such as those related to actin, adherens junction, and microtubule dynamics), development and differentiation pathways (such as hedgehog, Notch, TGF-β, and Wnt/β-catenin signaling pathways), immunology and inflammation pathways (such as those for B-cell receptor signaling, cytokine receptor signaling, inflammatory response, rheumatoid arthritis, T-cell activation, and TLR-induced immune response), neuroscience pathways (such as Alzheimer’s disease- and Parkinson’s disease-related signaling pathways) and translational control pathways (such as eIF2, eIF4/P70S6K, and mTOR signaling pathways).

Since genes and pathways responsible for the action of TCM are related to various cell functions, it is almost impossible to understand the mechanisms of action just by studying the mixture of chemicals. There are cases in which effective chemicals (such as those shown in Table 2) were analyzed in order to understand specific mechanisms, such as Bax signaling/apoptosis (2,4,3',5'-tetramethoxystilbene), ERK signaling/anti-atherosclerosis (brefeldin A), ERK signaling/anti-carcinogenesis (grifolin), estrogen signaling (ginsenosides F1/Rb1/Rg1/Rh1 and glycyrrhizin), estrogen signaling/carcinogenesis (3,3'-diindolylmethane), HSP70 (a 70 kilodalton heat shock protein) signaling/anti-carcinogenesis (paeoniflorin), NF-κB signaling/anti-carcinogenesis (quercetin), NF-κB signaling/anti-inflammation (ergosterol peroxide), NF-κB signaling/apoptosis (tanshinone IIA), NF-κB signaling/hypoxia (paeonol), Nrf2-antioxidant response element (ARE) signaling/chemoprevention (myricetin), PI3K-Akt signaling/chemoprevention (sulforaphane), PPAR-γ signaling/adipogenesis (aculeatin), reactive oxygen species (ROS) signaling/apoptosis (β-hydroxyisovalerylshikonin), Rho/ROCK signaling/cell migration (tanshinone IIA), skn-1 signaling/life-span extension (diallyl trisulfide), and tumor necrosis factor receptor 1 (TNFR1)-IGF-1R signaling/apoptosis (emodin). These signaling pathways are summarized in Figure 1.

3.2. Cell Functions Involved in the Action

The major cell functions analyzed by DMA for TCM include: adipogenesis, anti-atherosclerosis, anti-carcinogenesis, anti-inflammation, apoptosis, carcinogenesis, chemoprevention, hypoxia, and life-span extension (Table 2; Figure 1).

Adipogenesis is a cellular differentiation process in which preadipocytes are transformed into differentiated adipocyte cells, and involves features such as morphological change, growth arrest, lipogenic gene expression, and the production of hormones and growth factors (such as leptin and TNF-α). Among the components found in the extract of Toddalia asiatica, aculeatin was found to promote the differentiation of mouse 3T3-L1 preadipocytes into adipocytes [132]. DMA revealed the involvement of PPAR-γ target genes in the process of activation by aculeatin, which is not a ligand of PPAR-γ, suggesting the presence of additional signaling mechanisms.

Atherosclerosis is a chronic inflammatory response of white blood cells in arterial blood vessels, which is promoted by low-density lipoproteins (LDLs), carriers of cholesterol, and triglycerides, and results in the formation of atherosclerotic plaques that are rich in macrophages and foam cells. Estrogenic activity was detected by DMA-based gene expression profiling in the extract of Agaricus blazei, which was attributable to brefeldin A [138]. The extract has no estrogen receptor-dependent cell proliferation activity, while showing activation of estrogen signaling (such as activation of ERK, Akt and P70S6K) and beneficial effects for patients with high levels of oxidized LDLs (see Section 3.3).
Figure 1. Summary of actions and their mechanisms by the chemicals related to traditional Chinese medicine. The mechanisms of action by the chemicals originally identified or isolated from medicinal herbs, mushrooms and dietary plants (aculeatin, brefeldin A, ergosterol peroxide, grifolin, β-hydroxyisovalerylshikonin, paeonol, quercetin and tanshinone IIA) within the cytosol (blue area) or the nucleus (yellow area) are summarized. APP: amyloid precursor protein; CCL2: chemokine (C-C motif) ligand 2; ERK: extracellular-signal-regulated kinase; β-HIVS: β-hydroxyisovalerylshikonin; MAPK: mitogen-activated protein kinase; PPAR-γ: peroxisome proliferator-activated receptor γ; PXR: pregnane X receptor; Rb: retinoblastoma protein; TNFR: tumor necrosis factor receptor; and TRAP1: tumor necrosis factor receptor-associated protein 1.
Carcinogenesis, alternatively referred to as oncogenesis or tumorigenesis, is a process by which normal cells are transformed into cancer cells characterized by uncontrolled cell division; it involves a progression of changes at the cellular, genetic, and epigenetic levels. Several chemicals exhibiting anti-carcinogenic effects were isolated or identified from natural products, such as 3,3′-diindolylmethane from cruciferous vegetables [145], grifolin from *Albatrellus confluens* [153], paeoniflorin from *Paeonia lactiflora* [157], and quercetin from various dietary plants [161], and further analyzed by DMA. 3,3′-Diindolylmethane is estrogenic and shows gene expression profiles favoring tumor promotion [145]. Grifolin acts negatively against the cell cycle and cell growth through inhibiting ERK and Rb pathways, and downregulates the expression of *cyclin D1*, *cyclin E*, and *CDK4* (a gene for a cyclin-dependent kinase), and upregulates the expression of *CKI* (a CDK inhibitor gene) [153]. Paeoniflorin enhances the expression of HSP70, which helps to protect cells from stress, and modulates the expression of *CDC2*, *FOSL1*, and *EGR1*, regulators of cell growth and proliferation [161]. Quercetin, on the other hand, induces p53-independent apoptosis by enhancing the expression of death-receptor or TNFR signaling genes, such as the genes for caspase-10, DFF45, FAS, IκBα, IL1R (Interleukin-1 receptor), TNFR1, and TRAILR [171].

Inflammation is a protective response to cell injury, and involves the local vascular system, the immune system, and various cells within the injured tissue. Ergosterol peroxide produced by *Sarcodon aspratus* suppresses inflammatory response in macrophages by inhibiting TNF-α secretion and down-regulating the expression of interleukin1α/β (IL-1α/β) through pathways such as C/EBPβ, ERK, JNK, MAPK, and NF-κB [147].

Apoptosis is the process of programmed cell death that may occur in multicellular organisms in response to various stresses, such as heat, hypoxia, increased intracellular calcium concentration, nutrient deprivation, receptor–ligand binding, radiation, and viral infection. Several chemicals are related to the promotion of apoptosis and thus have been used as effective components in herbal medicine. Emodin extracted from the rhizomes of *Rheum palmatum* showed testicular toxicity, including the induction of apoptosis, most likely through pathways such as IGF-1, TGF/Wnt, and TNFR signaling [146]. β-Hydroxyisovalerylshikonin extracted from *Lithospermum erythrorhizon* is an inhibitor of protein-tyrosine kinases and induces apoptosis by suppressing TRAP1, a TNF-associated protein and a member of the HSPs, as well as the production of ROS [155]. Tanshinone IIA found in the root of *Salvia miltiorrhiza* induces peroxisome proliferator-activated receptor (PPAR)/NF-κB/CCL2-mediated apoptosis in leukemia cells [180]. 2,4,3′,5′-Tetramethoxystilbene extracted from fruit, berries, and grapes is a derivative of resveratrol and a strong inducer of apoptosis by increasing the expression of tubulin, stress response, and pro-apoptotic genes [178].

Chemoprevention refers to the administration of a medication, such as drugs and vitamins, for the purpose of preventing disease or infection, and various chemicals have been developed especially for cancer chemoprevention. Myricetin [158] and sulforaphane [177] isolated from dietary plants show chemopreventive activity against cancer through activating Nrf2-mediated antioxidant response or PI3K/Akt signaling pathways, respectively.

Hypoxia is a condition in which a cell is deprived of adequate oxygen supply and has been shown to stimulate various biological and physiological responses. Paeonol isolated from *Paeonia suffruticosa* induces the expression of hypoxia-inducible genes, including hypoxia-inducible factor 1 (HIF-1)-target genes, through suppressing the NF-κB signaling pathway and inhibiting amyloid precursor protein (APP) activity [162].

Life extension has been studied in terms of slowing down or reversing the processes of aging in order to extend both the maximum and the average lifespan, and the effects of anti-aging products, nutrition, physical fitness, skin care, hormone replacements, vitamins, supplements, and herbs have been examined. Diallyl trisulfide isolated from garlic increases the longevity of nematodes through activation of the pro-longevity transcription factor gene *skn-1* and the products of its target genes [144].

Conditions such as chronic (arthritis, asthma, cancer, diabetes, and viral diseases) and neurodegenerative (Parkinson’s and Alzheimer’s diseases) diseases have been treated with TCM [1],...
among which some were investigated by DMA and explored by animal tests and/or clinical studies to eventually achieve clinical applications. Other than the cell functions discussed above, the diseases with extensive impacts were also investigated. For example, antidepressant, anti-diabetic, anti-obesity, neuromodulation, and neuroprotection effects, and the treatments of neurological, Parkinson’s, and Alzheimer’s diseases associated with TMC and/or constituent herbs/mushrooms/dietary plants were studied by means of DMA (Table 1), or their effective components, such as ginsenosides (for diabetes), (−)-hydroxycitric acid (for obesity), obovatol (for neuroinflammation), and salvianolic acid B (for neuroprotection), were studied by means of DMA (Table 2).

3.3. Activities Found by DNA Microarray Assays (Silent Estrogens)

Activities found by DMA are often detected as cell signals in specific pathways, such as angiogenesis, ErbB/HER, MAPK, nuclear receptor, and ubiquitin/proteasome signaling pathways, and/or in cell functions, such as apoptosis, autophagy, cell cycle/DNA damage/cytoskeletal formation, cellular metabolism, chromatin/epigenesis regulation, development/differentiation, immunology/inflammation response, neurological diseases, and translational control [183]. While most of these cell signaling pathways and cell functions can be detected by other technologies, there might be some activities that can be detected exclusively by DMA. One such activity is by a group of estrogens, silent estrogens, which show estrogenic gene expression profiles without showing positive effects on cell proliferation [13].

Estrogen is a female hormone that is responsible for various biological and physiological activities, including receptor-mediated stimulation of the proliferation of cells in tissues such as the breast and ovary. Several chemicals and mixtures of chemicals, such as brefeldin A [138], licorice extracts [150], and oil degradation products [184], were found to show gene expression profiles similar to that for estrogen, although they did not stimulate the proliferation of estrogen receptor-positive breast cancer MCF-7 cells. Although the signaling pathway for cell proliferation could theoretically be separated from those for other cell functions, this separation has not been possible because most of the cells examined for estrogenic activity contain estrogen receptors and the technologies used were not suited to such a purpose. Recent findings about more complicated signaling pathways/networks, such as autocrine/paracrine/homeostatic networks and crosstalk/bypassing of cell signals, include pathways not necessarily involving cell proliferation or the cells containing estrogen receptors [185,186]. Thus, estrogenic activity can be detected even for silent estrogens because DMA can separate various signaling pathways, and the similarity of chemicals can be analyzed at the levels of gene expression and cell signaling.

4. Applications of DNA Microarray Assays for Traditional Chinese Medicine

Modernization of TCM has been discussed in association with several key issues, such as the material basis of TCM formulas, the quality evaluation system and evaluation of the efficiency and safety of TCM formulas; key technological tools in systems biology, such as those in genomics, interactomics, metabolomics, phenomics, and proteomics, could also be used to understand the chemome of TCM, an integrated world of the external TCM system and the internal human body [2]. TCMs, such as Beimu (Fritillaria spp.), Chishao (Paeonia spp.), Chuanxiong (Ligusticum chuanxiong), Chuipencao (Sedum sarmentosum), Danngui (Angelica sinensis), Danshen (Salvia miltiorrhiza), Dongchongxiaocao (Cordyceps sinensis), Ezhu/Yujin (rhizome and radix of Curcuma), Guanghuoxiang (Pogostemon cablin), Huangqi (Astragalus spp.), Jinyinhua (Lonicera japonica), Juhua (Chrysanthemum morifolium), Lingzhi (Ganoderma spp.), Sanqi (Panax notoginseng), Wuweizi (Schisandra chinensis), and Yingyanghuo (Epimedium spp.), were analyzed by biophysical techniques such as capillary electrophoresis, gas chromatography, HPLC, mass spectrometry (MS), thin-layer chromatography (TLC), ultra-performance liquid chromatography (UPLC), and ultraviolet/near-infrared spectrometry, by molecular biological techniques such as genomic PCR and RT-PCR, or by immunological assays such as enzyme-linked immunosorbent
assay (ELISA) for screening and/or quality control of effective components, which include alkaloids, cyanophoric glycosides, ergosterol, essential oils, flavonoids, iridoid glycosides, lignans, paenoniflorin, phenolic acids, saponins, steroids, sugars/polysaccharides, and triterpenoids [5].

Chinese medicinal plants were analyzed by DNA-based technologies, such as those detecting amplified fragment length polymorphism (AFLP), cleaved amplified polymorphic sequence (CAPS), inter-simple sequence repeat (ISSR), random amplified polymorphic DNA (RAPD), restriction fragment length polymorphism (RFLP), and simple sequence repeat (SSR), and those by amplification refractory mutation system (ARMS), DNA amplification fingerprinting (DAF), hybridization, microarray assay and sequencing [8], or by assays at the cell/tissue/animal levels, such as gene knockout and cell membrane chromatography and transgenics [187].

The literature surveyed for transcriptomics using DMA in the study of 297 frequently used medicinal herbs in China showed that most of the studies focused on finding their biological effects [10]. However, there are cases where DMA was applied to screen effective components and for quality control of TCM. In this section, we discuss how DMA has been used for quality control of TCM.

Additional applications of effective chemicals in TCM analyzed by DMA include patent filing, drug discovery, and clinical trials. An effective chemical identified and characterized by these applications can be patented as a new chemical, or otherwise as a known chemical with a new application.

4.1. DNA Microarray Assays for Quality Control of Traditional Chinese Medicine

DMA has been used to detect and evaluate various activities of pure chemicals and mixtures of chemicals [13,188]. When DMA was applied for the study of TCM, gene sets specific to herbs were selected. For example, a set of 55 genes were screened by DMA in order to understand the effect of Qingfei Xiaoyan Wan formula on asthma by the regulation of gene/protein networks [80]. A set of 92 genes was found to be differentially regulated by Toki-shakuyaku-san, a formula effective for circulation problems [89]. A set of nine marker genes was initially screened by DMA and subsequently confirmed by RT-PCR to assess the batch-to-batch consistency of the biological effects of ISF-1, a formula used for the management of post-stroke disorders [6].

Once gene sets have been selected, they can be used for screening and/or quality control of the herbs. For example, DMA was used to screen TCM species with inhibitory effects on Cytochrome P450 (CYP450) intended to treat HIV infection [189]. High-throughput DMA were applied to screen for anti-mitotic effects (independent of toxicity) on the proliferation of MDA-MB-231 cells from 897 aqueous extracts of commonly used natural products, and less than 1.34% of the extracts tested showed growth inhibitory properties at a concentration of less than 0.0183 mg/mL [27]. The DMA based on the yeast transcriptome was used for quality control of the extracts of *Equisetum arvense* [30].

Specific activity was examined to evaluate the quality of materials in food and supplements. For example, estrogenic activity was examined by DMA using a customized DNA microarray containing 172 estrogen-responsive genes in order to evaluate food materials, such as phytoestrogens [127] and ginsenosides [148], and for the extracts of plants and mushrooms, such as soybeans [127], *Glycyrrhiza glabra* [150], and *Agaricus blazei* [138]. The estrogen-responsive genes were further classified into six functional groups (enzymes, signaling, proliferation, transcription, transport, and others) and some showed preferences for specific groups [183].

4.2. Protocols of DNA Microarray Assays for Quality Control

Schemes of new DMA-based protocols for quality control of herbal extracts are summarized in Figure 2. A simplified protocol is based on gene expression profiles of different sources of herbal extracts (A1 to A5), which are compared with that of a standard (S) by correlation coefficients (R-values) based on linear regression (Figure 2A). Deviations (such as in A3, Figure 2A) can be detected by comparing R-values. While gene sets for expression profiling can be used without selection (Figure 2A), the genes having specific cell functions could be used to improve the level of quality
control (Figure 2B,C), where the gene sets (G1 to G3) can be selected arbitrarily, such as those showing stable (G1), less stable (G2) or unstable (G3) reproducibility when various lots (A1 and A2) of the herbal extracts are compared with a standard (Figure 2B). Alternatively, gene sets can be selected according to gene functions (Figure 2C), where profiling can be performed with functionally grouped genes (F1 to F3) to give a protocol of efficacy-based quality control of herbal extracts. The advantages for using these protocols are that: (1) cell function-based gene expression profiling is good for efficacy-based quality control; (2) gene sets can be selected depending on the purpose; and (3) various activities can be monitored by different gene sets.

**Figure 2.** Quality control of herbal components by gene expression profiling. Examples of application of DMA for quality control of TCM are summarized. (A) A simplified protocol of quality control of herbal extracts. Gene expression profiles for different sources of herbal extracts (A1 to A5) are compared with that of a standard (S) using correlation coefficients (R-values) based on linear regression. A case of deviation (A3) can be detected by comparing R-values for the profiles of the genes appropriately selected. (B) Selection of gene sets for gene expression profiling-based quality control. The degree of stability in quality control can be influenced and controlled by selecting arbitrarily grouped genes (G1 to G3), which show stable (G1), less stable (G2) or unstable (G3) reproducibility upon comparing various lots (A1 and A2) of the herbal extracts with a standard (S). (C) Selection of gene sets for gene function-based quality control. The profiling shown in (B) can be performed with functionally grouped genes (F1 to F3) to give a protocol of efficacy-based quality control of herbal extracts.
5. Conclusions and Perspectives

Owing to the progress of new biotechnological tools, new approaches have been developed, including systems biology, signal transduction study, and RNA-sequencing-based whole genome/exome analysis, which provide us with massive amounts of omics data. However, we still do not know how to use these tools effectively. For example, we now know a number of chemicals showing estrogenic activity and the number is steadily increasing because they affect cells, tissues, and organs through complex and novel pathways of cell signaling, such as intracellular signal transduction, signal crosstalk/bypassing, and intercellular networks of autocrine/paracrine signaling [185,186]. This complex status would be the same as in the study and the application of TCM because, since estrogenic activity is one of the most important activities of effective components in herbs and has been shown to affect the human body, the findings about estrogen would be true for more complex statuses, which include other hormones and growth factors. Chemicals having other hormonal and growth-factor activities could show such complexities, and thus new approaches are needed to understand the effects of chemicals. Other than the pharmacological use of chemicals, DNA-based gene expression profiling and pathway-based testing of chemicals have been developed for the diagnosis of diseases and risk assessment of endocrine disruptors, where the development of new types of diagnostic tool is in progress, such as the in vitro diagnostic multivariate index assay (IVDMIA), and toxicity pathway-based risk management protocols, such as those proposed by the U.S. National Research Council [190]. Thus, a pathway-based evaluation of beneficial effects and the assessment of potential risks by means of omics technologies are needed for the study and development of TCM.

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References
1. Liu, C.; Tseng, A.; Yang, S. Chinese Herbal Medicine: Modern Applications of Traditional Formulas; CRC Press: Boca Raton, FL, USA, 2007.
2. Luo, G.; Wang, Y.; Liang, Q.; Liu, Q. Systems Biology for Traditional Chinese Medicine; John Wiley & Sons: Hoboken, NJ, USA, 2012.
3. Hard to swallow. Nature 2007, 448, 105–106.
4. Shang, A.; Huwiler, K.; Nartey, L.; Jüni, P.; Egger, M. Placebo-controlled trials of Chinese herbal medicine and conventional medicine comparative study. Int. J. Epidemiol. 2007, 36, 1086–1092. [CrossRef] [PubMed]
5. Li, S.-P.; Wang, Y.-T. Pharmacological Activity-Based Quality Control of Chinese Herbs; Nova Science Publishers: New York, NY, USA, 2008.
6. Rong, J.; Tilton, R.; Shen, J.; Ng, K.M.; Liu, C.; Tam, P.K.; Lau, A.S.; Cheng, Y.C. Genome-wide biological response fingerprinting (BioReF) of the Chinese botanical formulation ISF-1 enables the selection of multiple marker genes as a potential metric for quality control. J. Ethnopharmacol. 2007, 113, 35–44. [CrossRef] [PubMed]
7. Hudson, J.; Altamirano, M. The application of DNA micro-arrays (gene arrays) to the study of herbal medicines. J. Ethnopharmacol. 2006, 108, 2–15. [CrossRef] [PubMed]
8. Heubl, G. New aspects of DNA-based authentication of Chinese medicinal plants by molecular biological techniques. Planta Med. 2010, 76, 1963–1974. [CrossRef] [PubMed]
9. Naoghare, P.K.; Song, J.M. Chip-based high-throughput screening of herbal medicines. Comb. Chem. High Throughput Screen. 2010, 13, 923–931. [CrossRef] [PubMed]
10. Lo, H.Y.; Li, C.C.; Huang, H.C.; Lin, L.J.; Hsiang, C.Y.; Ho, T.Y. Application of transcriptomics in Chinese herbal medicine studies. J. Tradit. Complement. Med. 2012, 2, 105–114. [CrossRef]
11. Sarwat, M.; Yamdagni, M.M. DNA barcoding, microarrays and next generation sequencing: Recent tools for genetic diversity estimation and authentication of medicinal plants. Crit. Rev. Biotechnol. 2016, 36, 191–203. [CrossRef] [PubMed]

12. National Center for Complementary and Integrative Health. Traditional Chinese Medicine: An Introduction. 2013. Available online: https://nccih.nih.gov/health/whatiscam/chinesemed.htm (accessed on 26 January 2017).

13. Kiyama, R.; Zhu, Y. DNA microarray-based gene expression profiling of estrogenic chemicals. Cell. Mol. Life Sci. 2014, 71, 2065–2082. [CrossRef] [PubMed]

14. Einbond, L.S.; Soffritti, M.; Espositi, D.D.; Wu, H.A.; Tibaldi, E.; Lauriola, M.; He, K.; Park, T.; Su, T.; Huggins, L.; et al. Pharmacological mechanisms of black cohosh in Sprague-Dawley rats. Fitoterapia 2012, 83, 461–468. [CrossRef] [PubMed]

15. Zhao, H.; Deneau, J.; Che, G.O.; Li, S.; Vagnini, F.; Azadi, P.; Sonon, R.; Ramjit, R.; Lee, S.M.; Bojanowski, K. Angelica sinensis isolate SBD.4: Composition, gene expression profiling, mechanism of action and effect on wounds, in rats and humans. Eur. J. Dermatol. 2012, 22, 58–67. [PubMed]

16. Yang, N.S.; Shyur, L.F.; Chen, C.H.; Wang, S.Y.; Tzeng, C.M. Medicinal herb extract and a single-compound drug confer similar complex pharmacogenomic activities in MCF-7 cells. J. Biomed. Sci. 2004, 11, 418–422. [CrossRef] [PubMed]

17. Zhang, Q.; Wei, F.; Fong, C.C.; Yu, W.K.; Chen, Y.; Koon, C.M.; Lau, K.M.; Leung, P.C.; Lau, C.B.; Fung, K.P.; et al. Transcriptional profiling of human skin fibroblast cell line HS27 induced by herbal formula Astragali radix and Rehmanniae radix. J. Ethnopharmacol. 2011, 138, 668–675. [CrossRef] [PubMed]

18. Kiela, P.R.; Midura, A.J.; Kuscuoglu, N.; Jolad, S.D.; Solyom, A.M.; Besselsen, D.G.; Timmermann, B.N.; Ghishan, F.K. Effects of Bosweilla serrata in mouse models of chemically induced colitis. Am. J. Physiol. Gastrointest. Liver Physiol. 2005, 288, G798–G808. [CrossRef] [PubMed]

19. El-Readi, M.Z.; Eid, S.; Ashour, M.L.; Tahran, A.; Wink, M. Modulation of multidrug resistance in cancer cells by chelidonine and Chelidonium majus alkaloids. Phytomedicine 2013, 20, 282–294. [CrossRef] [PubMed]

20. Kim, K.S.; Lim, D.J.; Yang, H.J.; Choi, E.K.; Shin, M.H.; Ahn, K.S.; Jung, S.H.; Um, J.Y.; Jung, H.J.; Lee, J.H.; et al. The multi-targeted effects of Chrysanthemum herb extract against Escherichia coli O157:H7. Phytother. Res. 2013, 27, 1398–1406. [CrossRef] [PubMed]

21. Shimoda, H.; Tanaka, J.; Takahara, Y.; Takemoto, K.; Shan, S.J.; Su, M.H. The hypocholesterolemic effects of Cistanche tubulosa extract, a Chinese traditional crude medicine, in mice. Am. J. Chin. Med. 2009, 37, 1125–1138. [CrossRef] [PubMed]

22. Cheng, W.Y.; Wu, S.L.; Hsiang, C.Y.; Li, C.C.; Lai, T.Y.; Lo, H.Y.; Shen, W.S.; Lee, C.H.; Chen, J.C.; Wu, H.C.; et al. Relationship Between San-Huang-Xie-Xin-Tang and its herbal components on the gene expression profiles in HepG2 cells. Am. J. Chin. Med. 2008, 36, 783–797. [CrossRef] [PubMed]

23. Iizuka, N.; Oka, M.; Yamamoto, K.; Tangoku, A.; Lauriola, M.; He, K.; Park, T.; Su, T.; Huggins, L.; et al. Pharmacological mechanisms of black cohosh in Sprague-Dawley rats. Fitoterapia 2012, 83, 461–468. [CrossRef] [PubMed]

24. Wang, C.Y.; Chiao, M.T.; Yen, P.J.; Huang, W.C.; Hou, C.C.; Chien, S.C.; Yeh, K.C.; Yang, W.C.; Shyur, L.F.; Yang, N.S. Modulatory effects of Echinacea purpurea extracts on human dendritic cells: A cell- and gene-based study. Genomics 2006, 88, 801–808. [CrossRef] [PubMed]
63. Jedinak, A.; Sliva, D. Novel medicinal mushroom blend suppresses growth and invasiveness of human breast cancer cells through p53-dependent as well as p53-independent pathway. *Int. J. Oncol.* 2008, 33, 1307–1313. [PubMed]
Zhao, Z.; Miao, Y.; Pan, P.; Cheng, B.; Bai, G.; Wu, H. Qingfei Xiaoyan Wan alleviates asthma through polyaccharopeptide I’m-Yunity and Danshen and their combination. Int. J. Oncol. 2006, 29, 1215–1222. [CrossRef] [PubMed]

Hsieh, T.C.; Wu, J.M. Differential control of growth, cell cycle progression, and gene expression in human estrogen receptor positive MCF-7 breast cancer cells by extracts derived from polysaccharopeptide I’m-Yunity and Danshen and their combination. Int. J. Oncol. 2006, 29, 1215–1222. [CrossRef] [PubMed]

Yamakawa, J.; Ishigaki, Y.; Takahashi, T.; Yoshida, J.; Moriya, J.; Takata, T.; Tatsuno, T.; Sasaki, K.; Ohta, T.; et al. The Kampo medicines Orendegokuto, Bofutsushosan and Boiogito have different activities to regulate gene expressions in differentiated rat white adipocytes: Comprehensive analysis of genetic profiles. Biol. Pharm. Bull. 2008, 31, 2083–2089. [CrossRef] [PubMed]

Kim, J.M.; Kim, H.G.; Han, J.M.; Lee, J.S.; Lee, H.W.; Choi, M.K.; Son, C.G. The herbal formula CGX ameliorates the expression of vascular endothelial growth factor in alcoholic liver fibrosis. J. Ethnopharmacol. 2013, 150, 892–900. [CrossRef] [PubMed]

Choi, R.C.; Gao, Q.T.; Cheung, A.W.; Zhu, J.T.; Lau, F.T.; Li, J.; Li, W.Z.; Chu, G.K.; Duan, R.; Cheung, J.K.; et al. A Chinese herbal decoction, Danggui Buxue Tang, stimulates proliferation, differentiation and gene expression of cultured osteosarcoma cells: Genomic approach to reveal specific gene activation. Evid. Based Complement. Altern. Med. 2011, 2011, 307548. [CrossRef] [PubMed]

Zeng, X.; Yang, J.; Yang, X.; Hong, D.; Wu, L.; Yu, J. Effect of Guanxin No.2 decoction on gene expression in different areas of the myocardial infarcted heart of rats using microarray technology. J. Pharm. Pharmacol. 2009, 61, 213–219. [CrossRef] [PubMed]

Tohda, M.; Hayashi, H.; Sukma, M.; Tanaka, K. BNIP-3: A novel candidate for an intrinsic depression-related factor found in NG108-15 cells treated with Hochu-ekki-to, a traditional oriental medicine, or typical antidepressants. Neurosci. Res. 2008, 62, 1–8. [CrossRef] [PubMed]

Matsumoto, T.; Noguchi, M.; Hayashi, O.; Makino, K.; Yamada, H. Hochuekkito, a Kampo (traditional Japanese herbal) Medicine, Enhances Mucosal IgA Antibody Response in Mice Immunized with Antigen-entrapped Biodegradable Microparticles. Evid. Based Complement. Altern. Med. 2010, 7, 69–77. [CrossRef] [PubMed]

Zheng, Y.; Cheng, X.R.; Zhou, W.X.; Zhang, Y.X. Gene expression patterns of hippocampus and cerebral cortex of senescence-accelerated mouse treated with Huang-Lian-Jie-Du decoction. Neurosci. Lett. 2008, 439, 119–124. [CrossRef] [PubMed]

Sakaida, I.; Tsuchiya, M.; Kawaguchi, K.; Kimura, T.; Terai, S.; Okita, K. Herbal medicine Inchin-ko-to (TJ-135) prevents liver fibrosis and enzyme-altered lesions in rat liver cirrhosis induced by a choline-deficient l-amino acid-defined diet. J. Hepatol. 2003, 38, 762–769. [CrossRef]

Zheng, H.C.; Noguchi, A.; Makino, K.; Yamada, H. Hochuekkito, a Kampo (traditional Japanese herbal) Medicine, Enhances Mucosal IgA Antibody Response in Mice Immunized with Antigen-entrapped Biodegradable Microparticles. Evid. Based Complement. Altern. Med. 2010, 7, 69–77. [CrossRef] [PubMed]

Dong, F.X.; Zhang, X.Z.; Wu, F.; He, L.Q. The effects of Kangxianling on renal fibrosis as assessed with a customized gene chip. J. Tradit. Chin. Med. 2012, 32, 229–233. [CrossRef] [PubMed]

Hayasaki, T.; Sakurai, M.; Hayashi, T.; Murakami, K.; Hanawa, T. Analysis of pharmacological effect and molecular mechanisms of a traditional herbal medicine by global gene expression analysis: An exploratory study. J. Clin. Pharm. Ther. 2007, 32, 247–252. [CrossRef] [PubMed]

Bonham, M.J.; Galkin, A.; Montgomery, B.; Stahl, W.L.; Agus, D.; Nelson, P.S. Effects of the herbal extract PC-SPES on microtubule dynamics and paclitaxel-mediated prostate tumor growth inhibition. J. Natl. Cancer Inst. 2002, 94, 1641–1647. [CrossRef] [PubMed]

Hu, Y.; Chen, X.; Lin, H.; Hu, Y.; Mu, X. Study on the antiendotoxin action of Pulsatillae Decoction using an Affymetrix rat genome array. Cell Immunol. 2009, 257, 32–37. [CrossRef] [PubMed]

Zhao, Z.; Miao, Y.; Pan, P.; Cheng, B.; Bai, G.; Wu, H. Qingfei Xiaoyan Wan alleviates asthma through multi-target network regulation. BMC Complement. Altern. Med. 2013, 13, 206. [CrossRef] [PubMed]
81. Ji, G.; Wang, L.; Zhang, S.H.; Liu, J.W.; Zheng, P.Y.; Liu, T. Effect of Chinese medicine Qinggan Huoxuefang on inducing HSC apoptosis in alcoholic liver fibrosis rats. World J. Gastroenterol. 2006, 12, 2047–2052. [CrossRef] [PubMed]

82. Watanabe, T.; Yamamoto, T.; Yoshiida, M.; Fujiwara, K.; Kageyama-Yahara, N.; Kuramoto, H.; Shimada, Y.; Kadowaki, M. The traditional herbal medicine saireito exerts its inhibitory effect on murine oxazolone-induced colitis via the induction of Th1-polarized immune responses in the mucosal immune system of the colon. Int. Arch. Allergy Immunol. 2010, 151, 98–106. [CrossRef] [PubMed]

83. Wang, J.Y.; Chiu, J.H.; Tsai, T.H.; Tsou, A.P.; Hu, C.P.; Chi, C.W.; Yeh, S.F.; Lui, W.Y.; Wu, C.W.; Chou, C.K. Gene expression profiling predicts liver responses to a herbal remedy after partial hepatectomy in mice. Int. J. Mol. Med. 2005, 16, 221–231. [CrossRef] [PubMed]

84. Lee, H.; Bae, S.; Yoon, Y. The WNT/β-catenin pathway mediates the anti-adipogenic mechanism of SH21B, a traditional herbal medicine for the treatment of obesity. J. Ethnopharmacol. 2011, 133, 788–795. [CrossRef] [PubMed]

85. Wen, Z.; Wang, Z.; Wang, S.; Ravula, R.; Yang, L.; Xu, J.; Wang, C.; Zuo, Z.; Chow, M.S.; Shi, L.; et al. Discovery of molecular mechanisms of traditional Chinese medicinal formula Si-Wu-Tang using gene expression microarray and connectivity map. PLoS ONE 2011, 6, e18278. [CrossRef] [PubMed]

86. Fang, Z.; Lu, B.; Liu, M.; Zhang, M.; Yi, Z.; Wen, C.; Shi, T. Evaluating the pharmacological mechanism of Chinese medicine Si-Wu-Tang through multi-level data integration. PLoS ONE 2013, 8, e72334. [CrossRef] [PubMed]

87. Sun, Y.; Lee, S.M.; Wong, Y.M.; Lau, C.P.; Shaw, P.C.; Qin, L.; Leung, P.C.; Fung, K.P. Dosing effects of an antiosteoporosis herbal formula—A preclinical investigation using a rat model. Phytother. Res. 2008, 22, 267–273. [CrossRef] [PubMed]

88. Cheng, H.M.; Li, C.C.; Chen, C.Y.; Lo, H.Y.; Cheng, W.Y.; Lee, C.H.; Yang, S.Z.; Wu, S.L.; Hsiang, C.Y.; Ho, T.Y. Application of bioactivity database of Chinese herbal medicine on the therapeutic prediction, drug development, and safety evaluation. J. Ethnopharmacol. 2010, 132, 429–437. [CrossRef] [PubMed]

89. Kawamura, A.; Iacovidou, M.; Takaoka, A.; Soll, C.E.; Blumenstein, M. A polyacetylene compound from herbal medicine regulates genes associated with thrombosis in endothelial cells. Bioorg. Med. Chem. Lett. 2007, 17, 6879–6882. [CrossRef] [PubMed]

90. Sakai, R.; Irie, Y.; Murata, T.; Ishige, A.; Anjiki, N.; Watanabe, K. Toki-to protects dopaminergic neurons in the substantia nigra from neurotoxicity of MPTP in mice. Phytother. Res. 2007, 21, 868–873. [CrossRef] [PubMed]

91. Pan-Hammarström, Q.; Wen, S.; Hammarström, L. Cytokine gene expression profiles in human lymphocytes induced by a formula of traditional Chinese medicine, vigconic VI-28. J. Interferon Cytokine Res. 2006, 26, 628–636. [CrossRef] [PubMed]

92. Zheng, C.; Feng, L.; Li, M.; Dong, C.; Zhang, W. Effects of Xiaojinglong decoction on gene expression profiles in a rat chronic obstructive pulmonary disease model. Biosci. Trends 2012, 6, 262–269. [CrossRef] [PubMed]

93. Song, J.; Chen, W.Y.; Wu, L.Y.; Zheng, L.P.; Lin, W.; Gao, D.; Kaptchuk, T.J.; Chen, K.J. A microarray analysis of angiogenesis modulation effect of Xuefu Zhuyu Decoction on endothelial cells. Chin. J. Integr. Med. 2012, 18, 502–506. [CrossRef] [PubMed]

94. Shin, J.S.; So, C.S.; Kim, Y.O.; Ahn, D.K.; Sharman, K.G.; Sharman, E.H. The herbal prescription youkongdan modulates rodent memory, ischemic damage and cortical mRNA gene expression. Int. J. Neurosci. 2004, 114, 1365–1388. [CrossRef] [PubMed]

95. Zhang, Z.; Wang, Y.; Yao, R.; Li, J.; Yan, Y.; La Regina, M.; Lemon, W.L.; Grubbs, C.J.; Lubet, R.A.; You, M. Cancer chemopreventive activity of a mixture of Chinese herbs (antitumor B) in mouse lung tumor models. Oncogene 2004, 23, 3841–3850. [CrossRef] [PubMed]

96. Bonnet-Duquennoy, M.; Dumas, M.; Debacker, A.; Lazou, K.; Talboulset, S.; Franchi, J.; Heusèle, C.; André, P.; Schnebert, S.; Bonté, F.; et al. Transcriptional effect of an Aframomum angustifolium seed extract on human cutaneous cells using low-density DNA chips. J. Cosmet. Dermatol. 2007, 6, 128–134. [CrossRef] [PubMed]

97. Su, C.C.; Chen, G.W.; Tan, T.W.; Lin, J.G.; Chung, J.G. Crude extract of garlic induced caspase-3 gene expression leading to apoptosis in human colon cancer cells. In Vivo 2006, 20, 85–90. [PubMed]

98. Frantz, D.J.; Hughes, B.G.; Nelson, D.R.; Murray, B.K.; Christensen, M.J. Cell cycle arrest and differential gene expression in HT-29 cells exposed to an aqueous garlic extract. Nutr. Cancer 2000, 38, 255–264. [CrossRef] [PubMed]
99. Jung, M.; Triebel, S.; Anke, T.; Richling, E.; Erkel, G. Influence of apple polyphenols on inflammatory gene expression. Mol. Nutr. Food Res. 2009, 53, 1263–1280. [CrossRef] [PubMed]

100. Wang, Z.Q.; Ribničky, D.; Zhang, X.H.; Zuberi, A.; Raskin, I.; Yu, Y.; Cefalu, W.T. An extract of Artemisia dracunculus L. enhances insulin receptor signaling and modulates gene expression in skeletal muscle in KK-A(y) mice. J. Nutr. Biochem. 2011, 22, 71–78. [CrossRef] [PubMed]

101. Wang, L.S.; Dombkowski, A.A.; Seguin, C.; Rocha, C.; Cukovic, D.; Mukundan, A.; Henry, C.; Stoner, G.D. Mechanistic basis for the chemopreventive effects of black raspberries at a late stage of rat esophageal carcinogenesis. Mol. Carcinogen. 2011, 50, 291–300. [CrossRef] [PubMed]

102. Adams, L.S.; Kanaya, N.; Phung, S.; Liu, Z.; Chen, S. Whole blueberry powder modulates the growth and metastasis of MDA-MB-231 triple negative breast tumors in nude mice. J. Nutr. 2011, 141, 1805–1812. [CrossRef] [PubMed]

103. Furniss, C.S.; Bennett, R.N.; Bacon, J.R.; LeGall, G.; Mithen, R.F. Polyamine metabolism and transforming growth factor-β signaling are affected in Caco-2 cells by differentially cooked broccoli extracts. J. Nutr. 2008, 138, 1840–1845. [PubMed]

104. Suzuki, T.; Kumazoe, M.; Kim, Y.; Yamashita, S.; Nakahara, K.; Tsukamoto, S.; Sasaki, M.; Hagihara, T.; Tsurudome, Y.; Huang, Y.; et al. Green tea extract containing a highly absorbent catechin prevents diet-induced lipid metabolism disorder. Sci. Rep. 2013, 3, 2749. [CrossRef] [PubMed]

105. Klenow, S.; Jahns, F.; Pool-Zobel, B.L.; Glei, M. Does an extract of carob (Ceratonia siliqua) have chemopreventive potential related to oxidative stress and drug metabolism in human colon cells? J. Agric. Food Chem. 2009, 57, 2999–3004. [CrossRef] [PubMed]

106. Hwang, J.S.; Yoo, H.J.; Song, H.J.; Kim, K.K.; Chun, Y.J.; Matsu, T.; Kim, H.B. Inflammation-related signaling pathways implicating TGFβ are revealed in the expression profiling of MCF7 cell treated with fermented soybean, chungkookjang. Nutr. Cancer 2011, 63, 645–652. [CrossRef] [PubMed]

107. Salas, A.; Subirada, F.; Pérez-Enciso, M.; Blanch, F.; Jeusette, I.; Romano, V.; Torre, C. Plant polyphenol intake alters gene expression in canine leukocytes. J. Nutrigenet. Nutrigenom. 2009, 2, 43–52. [CrossRef] [PubMed]

108. Leow, S.S.; Sekaran, S.D.; Sundram, K.; Tan, Y.; Sambanthamurthi, R. Gene expression changes in spleens and livers of tumour-bearing mice suggest delayed inflammation and attenuated cachexia in response to oil palm phenolics. J. Nutrigenet. Nutrigenom. 2013, 6, 305–326. [CrossRef] [PubMed]

109. Ishii, S.; Katsumura, T.; Shiozuka, C.; Ooyach, K.; Kawasaki, K.; Takigawa, S.; Fukushima, T.; Tokui, Y.; Kinoshita, M.; Ohnishi, M.; et al. Anti-inflammatory effect of buckwheat sprouts in lipopolysaccharide-activated human colon cancer cells and mice. Biosci. Biotechnol. Biochem. 2008, 72, 3148–3157. [CrossRef] [PubMed]

110. Watanabe, C.M.; Wolffram, S.; Ader, P.; Rimbach, G.; Packer, L.; Maguire, J.J.; Schultz, P.G.; Gohil, K. The in vivo neuromodulatory effects of the herbal medicine ginkgo biloba. Proc. Natl. Acad. Sci. USA 2001, 98, 6577–6580. [CrossRef] [PubMed]

111. Rimbach, G.; Wolffram, S.; Watanabe, C.; Packer, L.; Gohil, K. Effect of Ginkgo biloba (EGb 761) on differential gene expression. Pharmacopsychiatry 2003, 36 (Suppl. 1), S95–S99. [PubMed]

112. Yunoki, K.; Sasaki, G.; Tokuji, Y.; Kinoshita, M.; Naito, A.; Aida, K.; Ohnishi, M. Effect of dietary wine pomace extract and oleanolic acid on plasma lipids in rats fed high-fat diet and its DNA microarray analysis. J. Agric. Food Chem. 2008, 56, 12052–12058. [CrossRef] [PubMed]

113. Lefevere, M.; Wiles, J.E.; Zhang, X.; Howard, L.R.; Gupta, S.; Smith, A.A.; Ju, Z.Y.; DeLany, J.P. Gene expression microarray analysis of the effects of grape anthocyanins in mice: A test of a hypothesis-generating paradigm. Metabolism 2008, 57 (Suppl. 1), S52–S57. [CrossRef] [PubMed]

114. Bagchi, D.; Sen, C.K.; Ray, S.D.; Das, D.K.; Bagchi, M.; Preuss, H.G.; Vinson, J.A. Molecular mechanisms of cardioprotection by a novel grape seed proanthocyanidin extract. Mutat. Res. 2003, 523–524, 87–97. [CrossRef]

115. De Waard, W.J.; Aarts, J.M.; Peijnenburg, A.A.; Baykus, H.; Talms, E.; Punt, A.; de Kok, T.M.; van Schooten, F.J.; Hoogenboom, L.A. Gene expression profiling in Caco-2 human colon cells exposed to TCDD, benzo[a]pyrene, and natural Ah receptor agonists from cruciferous vegetables and citrus fruits. Toxicol. In Vitro 2008, 22, 396–410. [CrossRef] [PubMed]

116. Yang, S.P.; Wilson, K.; Kaw, A.; Raner, G.M. Effects of green tea extracts on gene expression in HepG2 and Cal-27 cells. Food Chem. Toxicol. 2006, 44, 1075–1081. [CrossRef] [PubMed]
117. Edmunds, S.J.; Roy, N.C.; Davy, M.; Cooney, J.M.; Barnett, M.P.; Zhu, S.; Park, Z.; Love, D.R.; Laing, W.A. Effects of kiwifruit extracts on colonic gene and protein expression levels in IL-10 gene-deficient mice. *Br. J. Nutr.* 2012, 108, 113–129. [CrossRef] [PubMed]

118. Wang, X.; Yuan, S.; Wang, J.; Lin, P.; Liu, G.; Lu, Y.; Zhang, J.; Wang, W.; Wei, Y. Anticancer activity of litchi fruit pericarp extract against human breast cancer in vitro and in vivo. *Toxicol. Appl. Pharmacol.* 2006, 215, 168–178. [CrossRef] [PubMed]

119. Bang, S.; Lee, D.; Kim, H.; Park, J.; Bahn, Y.S. Global transcriptome analysis of eukaryotic genes affected by gromwell extract. *J. Sci. Food Agric.* 2014, 94, 445–452. [CrossRef] [PubMed]

120. Castagnini, C.; Luceri, C.; Toti, S.; Bigagli, E.; Caderni, G.; Femia, A.P.; Giovannelli, L.; Lodovici, M.; Pirozzi, V.; Salvadori, M.; et al. Reduction of colonic inflammation in HLA-B27 transgenic rats by feeding Marie Ménard apples, rich in polyphenols. *Br. J. Nutr.* 2009, 102, 1620–1628. [CrossRef] [PubMed]

121. Kobori, M.; Nakayama, H.; Fukushima, K.; Ohnishi-Kameyama, M.; Ono, H.; Fukushima, T.; Akimoto, Y.; Masumoto, S.; Yukizaki, C.; Hoshi, Y.; et al. Bitter gourd suppresses lipopolysaccharide-induced inflammatory responses. *J. Agric. Food Chem.* 2008, 56, 4004–4011. [CrossRef] [PubMed]

122. Croteau, D.L.; de Souza-Pinto, N.C.; Harboe, C.; Keijzers, G.; Zhang, Y.; Becker, K.; Sheng, S.; Bohr, V.A. DNA repair and the accumulation of oxidatively damaged DNA are affected by fruit intake in mice. *J. Gerontol. A Biol. Sci. Med. Sci.* 2010, 65, 1300–1311. [CrossRef] [PubMed]

123. Camargo, A.; Ruano, J.; Fernandez, J.M.; Parnell, L.D.; Jimenez, A.; Santos-Gonzalez, M.; Marin, C.; Perez-Martinez, P.; Uceda, M.; Lopez-Miranda, J.; et al. Gene expression changes in mononuclear cells in patients with metabolic syndrome after acute intake of phenol-rich virgin olive oil. *BMC Genom.* 2010, 11, 253. [CrossRef] [PubMed]

124. Izuchi, R.; Nakai, Y.; Takahashi, H.; Ushimaru, S.; Okada, S.; Abe, K. Hepatic gene expression of the insulin signaling pathway is altered by administration of persimmon peel extract: A DNA microarray study using type 2 diabetic Goto-Kakizaki rats. *J. Agric. Food Chem.* 2011, 59, 3320–3329. [CrossRef] [PubMed]

125. Zhang, J.; Kris-Etherton, P.M.; Thompson, J.T.; Vanden Heuvel, J.P. Effect of pistachio oil on gene expression of IFN-induced protein with tetratricopeptide repeats 2: A biomarker of inflammatory response. *Mol. Nutr. Food Res.* 2010, 54 (Suppl. 1), S83–S92. [CrossRef] [PubMed]

126. Im, R.; Mano, H.; Nakatani, S.; Shimizu, J.; Wada, M. Safety evaluation of the aqueous extract Kothala himbutu (*Salacia reticulata*) stem in the hepatic gene expression profile of normal mice using DNA microarrays. *Biosci. Biotechnol. Biochem.* 2008, 72, 3075–3083. [CrossRef] [PubMed]

127. Ise, R.; Han, D.; Takahashi, Y.; Terasaka, S.; Inoue, A.; Tanji, M.; Kiyama, R. Expression profiling of the estrogen responsive genes in response to phytoestrogens using a customized DNA microarray. *FEBS Lett.* 2005, 579, 1732–1740. [CrossRef] [PubMed]

128. Tokuiji, Y.; Akiyama, K.; Yunoki, K.; Kinoshita, M.; Sasaki, K.; Kobayashi, H.; Wada, M.; Ohnishi, M. Screening for beneficial effects of oral intake of sweet corn by DNA microarray analysis. *J. Food Sci.* 2009, 74, H197–H203. [CrossRef] [PubMed]

129. Prasad, R.C.; Herzog, B.; Boone, B.; Sims, L.; Waltner-Law, M. An extract of *Salvia officinalis* L. represses genes encoding hepatic gluconeogenic enzymes. *J. Ethnopharmacol.* 2005, 96, 295–301. [CrossRef] [PubMed]

130. Chia, Y.C.; Rajbanshi, R.; Calhoun, C.; Chiu, R.H. Anti-neoplastic effects of gallic acid, a major component of *Toona sinensis* leaf extract, on oral squamous carcinoma cells. *Molecules* 2010, 15, 8377–8389. [CrossRef] [PubMed]

131. Mykkänen, O.T.; Kalesnykas, G.; Adriaens, M.; Evelo, C.T.; Torrón, R.; Kaarniranta, K. Bilberries potentially alleviate stress-related C3H/HeJ mouse model. *PLoS ONE* 2012, 7, e45811. [CrossRef] [PubMed]

132. Zhang, J.; Zuo, G.; Bai, Q.; Wang, Y.; Yang, R.; Qiu, J. Microarray expression profiling of *Yersinia pestis* in response to berberine. *Planta Med.* 2009, 75, 396–398. [CrossRef] [PubMed]
135. Hara, A.; Iizuka, N.; Hamamoto, Y.; Uchimura, S.; Miyamoto, T.; Tsunedomi, R.; Miyamoto, K.; Hazama, S.; Okita, K.; Oka, M. Molecular dissection of a medicinal herb with anti-tumor activity by oligonucleotide microarray. *Life Sci.* 2005, 77, 991–1002. [CrossRef] [PubMed]

136. Moon, Y.J.; Brazeau, D.A.; Morris, M.E. Effects of flavonoids genistein and biochanin A on gene expression and their metabolism in human mammary cells. *Nutr. Cancer* 2007, 57, 48–58. [CrossRef] [PubMed]

137. Shen, Y.; Takahashi, M.; Byun, H.M.; Link, A.; Sharma, N.; Balaguer, F.; Leung, H.C.; Boland, C.R.; Goel, A. Boswellic acid induces epigenetic alterations by modulating DNA methylation in colorectal cancer cells. *Cancer Biol. Ther.* 2012, 13, 542–552. [CrossRef] [PubMed]

138. Oshida, K.; Hirakata, M.; Maeda, A.; Miyoshi, T.; Miyamoto, Y. Toxicological effect of emodin in mouse liver. *Toxicology Science* 2006, 91, 319–325. [CrossRef] [PubMed]

139. Pham, A.N.; Blower, P.E.; Alvarado, O.; Ravula, R.; Gout, P.W.; Huang, Y. Pharmacogenomic approach via microarrays. *Cancer Biol. Ther.* 2017, 13, 561–570. [CrossRef] [PubMed]

140. Yu, H.; Venkatesha, S.H.; Moudgil, K.D. Microarray-based gene expression profiling reveals the mediators and pathways involved in the anti-arthritic activity of Celastrus-derived Celastrol. *Int. Immunopharmacol.* 2012, 13, 499–506. [CrossRef] [PubMed]

141. Ramachandran, C.; Rodriguez, S.; Ramachandran, R.; Raveendran Nair, P.K.; Fonseca, H.; Khatib, Z.; Escalon, E.; Melnick, S.J. Expression profiles of apoptotic genes induced by curcumin in human breast cancer and mammary epithelial cell lines. *Anticancer Res.* 2005, 25, 3293–3302. [PubMed]

142. Meja, K.K.; Rajendrasozhan, S.; Adenuga, D.; Biswas, S.K.; Sundar, I.K.; Spooner, G.; Marwick, J.A.; Tilton, S.C.; Hendricks, J.D.; Orner, G.A.; Pereira, C.B.; Bailey, G.S.; Williams, D.E. Gene expression analysis during tumor enhancement by the dietary phytochemical, 3,3′-diindolylmethane, in rainbow trout. *Carcinogenesis* 2007, 28, 1589–1598. [CrossRef] [PubMed]

143. Lee, K.S.; Lee, B.S.; Semnani, S.; Avanesian, A.; Um, C.Y.; Jeon, H.J.; Seong, K.M.; Yu, K.; Min, K.J.; Jafari, M. Curcumin extends life span, improves health span, and modulates the expression of age-associated aging genes in *Drosophila melanogaster*. *Rejuvenation Res.* 2010, 13, 561–570. [CrossRef] [PubMed]

144. Powolny, A.A.; Singh, S.V.; Hubbard, A.; Fisher, A.L. The garlic constituent diallyl trisulfide increases the lifespan of *C. elegans* via skn-1 activation. *Exp. Gerontol.* 2011, 46, 441–452. [CrossRef] [PubMed]

145. Tilton, S.C.; Hendricks, J.D.; Orner, G.A.; Pereira, C.B.; Bailey, G.S.; Williams, D.E. Gene expression analysis during tumor enhancement by the dietary phytochemical, 3,3′-diindolylmethane, in rainbow trout. *Carcinogenesis* 2007, 28, 1589–1598. [CrossRef] [PubMed]

146. Oshida, K.; Hirakata, M.; Maeda, A.; Miyoshi, T.; Miyamoto, Y. Toxicological effect of emodin in mouse testicular gene expression profile. *J. Appl. Toxicol.* 2011, 31, 790–800. [CrossRef] [PubMed]

147. Kobori, M.; Yoshida, M.; Ohnishi-Kameyama, M.; Shinmoto, H. Ergosterol peroxide from an edible mushroom suppresses inflammatory responses in RAW264.7 macrophages and growth of HT29 colon adenocarcinoma cells. *Br. J. Pharmacol.* 2007, 150, 209–219. [CrossRef] [PubMed]

148. Dong, S.; Kiyama, R. Characterization of estrogentic activity of ginsenosides in MCF-7 cells using a customized DNA microarray. *Food Chem.* 2009, 113, 672–678. [CrossRef]

149. Xie, J.T.; Mehendale, S.R.; Li, X.; Quigg, R.; Wang, X.; Wang, C.Z.; Wu, J.A.; Aung, H.H.; Rue, P.A.; Bell, G.I.; et al. Anti-diabetic effect of ginsenoside Re in *ob/ob* mice. *Biochim. Biophys. Acta* 2005, 1740, 319–325. [CrossRef] [PubMed]

150. Dong, S.; Inoue, A.; Zhu, Y.; Tanji, M.; Kiyama, R. Activation of rapid signaling pathways and the subsequent transcriptional regulation for the proliferation of breast cancer MCF-7 cells by the treatment with an extract of *Glycyrrhiza glabra* root. *Food Chem. Toxicol.* 2007, 45, 2470–2478. [CrossRef] [PubMed]

151. Schröfelbauer, B.; Raffetseder, J.; Hauner, M.; Wolkerstorfer, A.; Ernst, W.; Szolar, O.H. Glycyrrhizin, the main active compound in liquorice, attenuates pro-inflammatory responses by interfering with membrane-dependent receptor signalling. *Biochem. J.* 2009, 421, 473–482. [CrossRef] [PubMed]

152. Lizarraga, D.; Vinardell, M.P.; Noé, V.; van Delft, J.H.; Alcarraz-Vizán, G.; van Breda, S.G.; Staal, Y.; Günther, U.L.; Carrigan, J.B.; Reed, M.A.; et al. A lyophilized red grape pomace containing proanthocyanidin-rich dietary fiber induces genetic and metabolic alterations in colon mucosa of female C57BL/6J mice. *J. Nutr.* 2011, 141, 1597–1604. [CrossRef] [PubMed]
153. Ye, M.; Luo, X.; Li, L.; Shi, Y.; Tan, M.; Weng, X.; Li, W.; Liu, J.; Cao, Y. Griffolin, a potential antitumor natural product from the mushroom *Albatrelus confluens*, induces cell-cycle arrest in G1 phase via the ERK1/2 pathway. *Cancer Lett.* **2007**, *258*, 199–207. [CrossRef] [PubMed]

154. Roy, S.; Shah, H.; Rink, C.; Khanna, S.; Bagchi, D.; Bagchi, M.; Sen, C.K. Transcriptome of primary adipocytes from obese women in response to a novel hydroxycitric acid-based dietary supplement. *DNA Cell Biol.* **2007**, *26*, 627–639. [CrossRef] [PubMed]

155. Masuda, Y.; Shima, G.; Aiuchi, T.; Horie, M.; Horii, K.; Nakajo, S.; Kajimoto, S.; Shibayama-Imazu, T.; Nakaya, K. Involvement of tumor necrosis factor receptor-associated protein 1 (TRAP1) in apoptosis induced by β-hydroxyisovalerylshikonin. *J. Biol. Chem.* **2004**, *279*, 42503–42515. [CrossRef] [PubMed]

156. Li, Z.; Li, D.; Huang, J.; Zhang, W.; Ding, Y.; Wang, S. Preparation of cardiovascular disease-related genes microarray and its application in exploring liguistrazine-induced changes in endothelial gene expression. *Pol. J. Pharmacol.* **2004**, *56*, 427–433. [PubMed]

157. Tan, H.L.; Moran, N.E.; Cichon, M.J.; Riedl, K.M.; Schwartz, S.J.; Erdman, J.W., Jr.; Pearl, D.K.; Thomas-Ahner, J.M.; Clinton, S.K. β-Carotene-9′,10′-oxygenase status modulates the impact of dietary tomato and lycopene on hepatic nuclear receptor-, stress-, and metabolism-related gene expression in mice. *J. Nutr.* **2014**, *144*, 431–439. [CrossRef] [PubMed]

158. Qin, S.; Chen, J.; Tanigawa, S.; Hou, D.X. Microarray and pathway analysis highlight Nrf2/ARE-mediated expression profiling by polyphenolic myricetin. *Mol. Nutr. Food Res.* **2013**, *57*, 435–446. [CrossRef] [PubMed]

159. Ock, J.; Han, H.S.; Hong, S.H.; Lee, S.Y.; Han, Y.M.; Kwon, B.M.; Suk, K. Obovatol attenuates microglia-mediated neuroinflammation by modulating redox regulation. *Br. J. Pharmacol.* **2010**, *159*, 1646–1662. [CrossRef] [PubMed]

160. Leow, S.S.; Sekaran, S.D.; Sundram, K.; Tan, Y.; Sambanthamurthi, R. Differential transcriptomic profiles effected by oil palm phenolics indicate novel health outcomes. *BMC Genom.* **2011**, *12*, 432. [CrossRef] [PubMed]

161. Salunga, T.L.; Tabuchi, Y.; Takasaki, I.; Feril, L.B., Jr.; Zhao, Q.L.; Ohtsuka, K.; Tsuneyama, K.; Kondo, T. Identification of genes responsive to paeoniflorin, a heat shock protein-inducing compound, in human leukemia U937 cells. *Int. J. Hyperth.* **2007**, *23*, 529–537. [CrossRef] [PubMed]

162. Su, S.Y.; Cheng, C.Y.; Tsai, T.H.; Hsiang, C.Y.; Ho, T.Y.; Hsieh, C.L. Paeonol attenuates H₂O₂-induced NF-κB-associated amyloid precursor protein expression. *Am. J. Chin. Med.* **2010**, *38*, 1171–1192. [CrossRef] [PubMed]

163. Huang, H.; Chang, E.J.; Lee, Y.; Kim, J.S.; Kang, S.S.; Kim, H.H. A genome-wide microarray analysis reveals anti-inflammatory target genes of paeoniflorin in macrophages. *Inflamm. Res.* **2008**, *57*, 189–198. [CrossRef] [PubMed]

164. Yu, W.S.; Jeong, S.J.; Kim, J.H.; Lee, H.J.; Song, H.S.; Kim, M.S.; Ko, E.; Lee, H.J.; Khil, J.H.; Jang, H.J.; et al. The genome-wide expression profile of 1,2,3,4,6-penta-O-galloyl-β-d-glucose-treated MDA-MB-231 breast cancer cells: Molecular target on cancer metabolism. *Mol. Cells* **2011**, *32*, 123–132. [CrossRef] [PubMed]

165. Xu, Z.; Le, K.; Moghaddasian, M.H. Long-term phytosterol treatment alters gene expression in the liver of apo E-deficient mice. *J. Nutr. Biochem.* **2008**, *19*, 545–554. [CrossRef] [PubMed]

166. Shuman Moss, L.A.; Jensen-Taubman, S.; Rubinstein, D.; Viole, G.; Stetler-Stevenson, W.G. Dietary intake of a plant phospholipid/lipid conjugate reduces lung cancer growth and tumor angiogenesis. *Carcinogenesis* **2014**, *35*, 1556–1563. [CrossRef] [PubMed]

167. Yoshikawa, R.; Yanagi, H.; Hashimoto-Tamaoki, T.; Morinaga, T.; Nakano, Y.; Noda, M.; Fujiwara, Y.; Okamura, H.; Yamamura, T. Gene expression in response to anti-tumour intervention by polysaccharide-K (PSK) in colorectal carcinoma cells. *Pol. J. Pharmacol.* **2004**, *56*, 427–433. [PubMed]

168. Li, Y.; Mei, L.; Niu, Y.; Sun, Y.; Huang, H.; Li, Q.; Kong, X.; Liu, L.; Li, Z.; Mei, Q. Low molecular weight apple polysaccharides induced cell cycle arrest in colorectal tumor. *Nutr. Cancer* **2012**, *64*, 439–463. [CrossRef] [PubMed]

169. Kachroo, P.; Ivanov, I.; Davidson, L.A.; Chowdhary, B.P.; Lupton, J.R.; Chapkin, R.S. Classification of diet-modulated gene signatures at the colon cancer initiation and progression stages. *Dig. Dis. Sci.* **2011**, *56*, 2595–2604. [CrossRef] [PubMed]

170. Morais, S.; Edvardsen, R.B.; Tocher, D.R.; Bell, J.G. Transcriptomic analyses of intestinal gene expression of juvenile Atlantic cod (*Gadus morhua*) fed diets with Camellina oil as replacement for fish oil. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* **2012**, *161*, 283–293. [CrossRef] [PubMed]
171. Youn, H.; Jeong, J.C.; Jeong, Y.S.; Kim, E.J.; Um, S.J. Quercetin potentiates apoptosis by inhibiting nuclear factor-κB signaling in H460 lung cancer cells. *Biol. Pharm. Bull.* 2013, *36*, 944–951. [CrossRef] [PubMed]

172. Nicholson, S.K.; Tucker, G.A.; Brameld, J.M. Effects of dietary polyphenols on gene expression in human vascular endothelial cells. *Proc. Nutr. Soc.* 2008, *67*, 42–47. [CrossRef] [PubMed]

173. Natoli, R.; Zhu, Y.; Valter, K.; Bisti, S.; Eells, J.; Stone, J. Gene and noncoding RNA regulation underlying photoreceptor protection: Microarray study of dietary antioxidant saffron and photobiomodulation in rat retina. *Mol. Vis.* 2010, *16*, 1801–1822. [PubMed]

174. Yang, Y.; Ge, P.J.; Jiang, L.; Li, F.L.; Zhu, Q.Y. Modulation of growth and angiogenic potential of oral squamous carcinoma cells in vitro using salvianolic acid B. *BMC Complement. Altern. Med.* 2011, *11*, 54. [CrossRef] [PubMed]

175. Ide, T.; Nakashima, Y.; Iida, H.; Yasumoto, S.; Katsuta, M. Lipid metabolism and nutrigenomics—Impact of sesame lignans on gene expression profiles and fatty acid oxidation in rat liver. *Forum Nutr.* 2009, *61*, 10–24. [PubMed]

176. Bateman, H.R.; Liang, Q.; Fan, D.; Rodriguez, V.; Lessner, S.M. Sparstolonin B inhibits pro-angiogenic functions and blocks cell cycle progression in endothelial cells. *PLoS ONE* 2013, *8*, e70500. [CrossRef] [PubMed]

177. Melchini, A.; Needs, P.W.; Mithen, R.F.; Traka, M.H. Enhanced in vitro biological activity of synthetic 2-(2-pyridyl) ethyl isothiocyanate compared to natural 4-(methylsulfinyl) butyl isothiocyanate. *J. Med. Chem.* 2012, *55*, 9682–9692. [CrossRef] [PubMed]

178. Aiyar, S.E.; Park, H.; Aldo, P.B.; Mor, G.; Gildea, J.J.; Miller, A.L.; Thompson, E.B.; Castle, J.D.; Kim, S.; Santen, R.J. TMS, a chemically modified herbal derivative of resveratrol, induces cell death by targeting Bax. *Breast Cancer Res. Treat.* 2010, *124*, 265–277. [CrossRef] [PubMed]

179. Li, W.; Sun, W.; Yang, C.H.; Hu, H.Z.; Jiang, Y.H. Tanshinone IIa protects against lipopolysaccharides-induced endothelial cell injury via Rho/Rho kinase pathway. *Chin. J. Integr. Med.* 2014, *20*, 216–223. [CrossRef] [PubMed]

180. Liu, C.; Li, J.; Wang, L.; Wu, F.; Huang, L.; Xu, Y.; Ye, J.; Xiao, B.; Meng, F.; Chen, S.; et al. Analysis of tanshinone IIA induced cellular apoptosis in leukemia cells by genome-wide expression profiling. *BMC Complement. Altern. Med.* 2012, *12*, 5. [CrossRef] [PubMed]

181. Chen, Y.; Zhang, X.M.; Han, F.M.; Du, P.; Xia, Q.S. Gene expression profile analyses of mice livers injured by Leigongteng. *World J. Gastroenterol.* 2007, *13*, 3619–3624. [CrossRef] [PubMed]

182. Inoue, A.; Tanji, M.; Kiyama, R. Focused Microarray Analysis: Characterization of Phenomes by Gene Expression Profiling. *Curr. Pharmacogenom.* 2004, *2*, 255–266. [CrossRef]

183. Kiyama, R.; Zhu, Y.; Kawaguchi, K.; Iitake, N.; Wada-Kiyama, Y.; Dong, S. Estrogen-responsive genes for environmental studies. *Environ. Technol. Innov.* 2014, *1*, 16–28. [CrossRef] [PubMed]

184. Zhu, Y.; Kitamura, K.; Maruyama, A.; Higashihara, T.; Kiyama, R. Estrogenic activity of bio-degradation products of C-heavy oil revealed by gene-expression profiling using an oligo-DNA microarray system. *Environ. Pollut.* 2012, *168*, 10–14. [CrossRef] [PubMed]

185. Kiyama, R.; Wada-Kiyama, Y. Estrogenic endocrine disruptors: Molecular mechanisms of action. *Environ. Int.* 2015, *83*, 11–40. [CrossRef] [PubMed]

186. Kiyama, R. Endocrine disruptor actions through receptor crosstalk. *Environ. Biotechnol.* 2016, *12*, 1–16.

187. Qv, X.Y.; Jiang, J.G.; Piao, J.H. Pharmacodynamic studies of Chinese medicine at levels of whole animal, cell and molecular models. *Curr. Med. Chem.* 2010, *17*, 4521–4537. [CrossRef] [PubMed]

188. Tanji, M.; Kiyama, R. Expression profiling of estrogen responsive genes using genomic and proteomic techniques for the evaluation of endocrine disruptors. *Curr. Pharmacogenom.* 2004, *2*, 255–266. [CrossRef]

189. Lee, S.S.; Zhang, B.; He, M.L.; Chang, V.S.; Kung, H.F. Screening of active ingredients of herbal medicine for interaction with CYP450 3A4. *Phytother. Res.* 2007, *21*, 1096–1099. [CrossRef] [PubMed]

190. National Research Council. *Toxicity Testing in the 21st Century: A Vision and a Strategy*; National Academies Press: Washington, DC, USA, 2007.