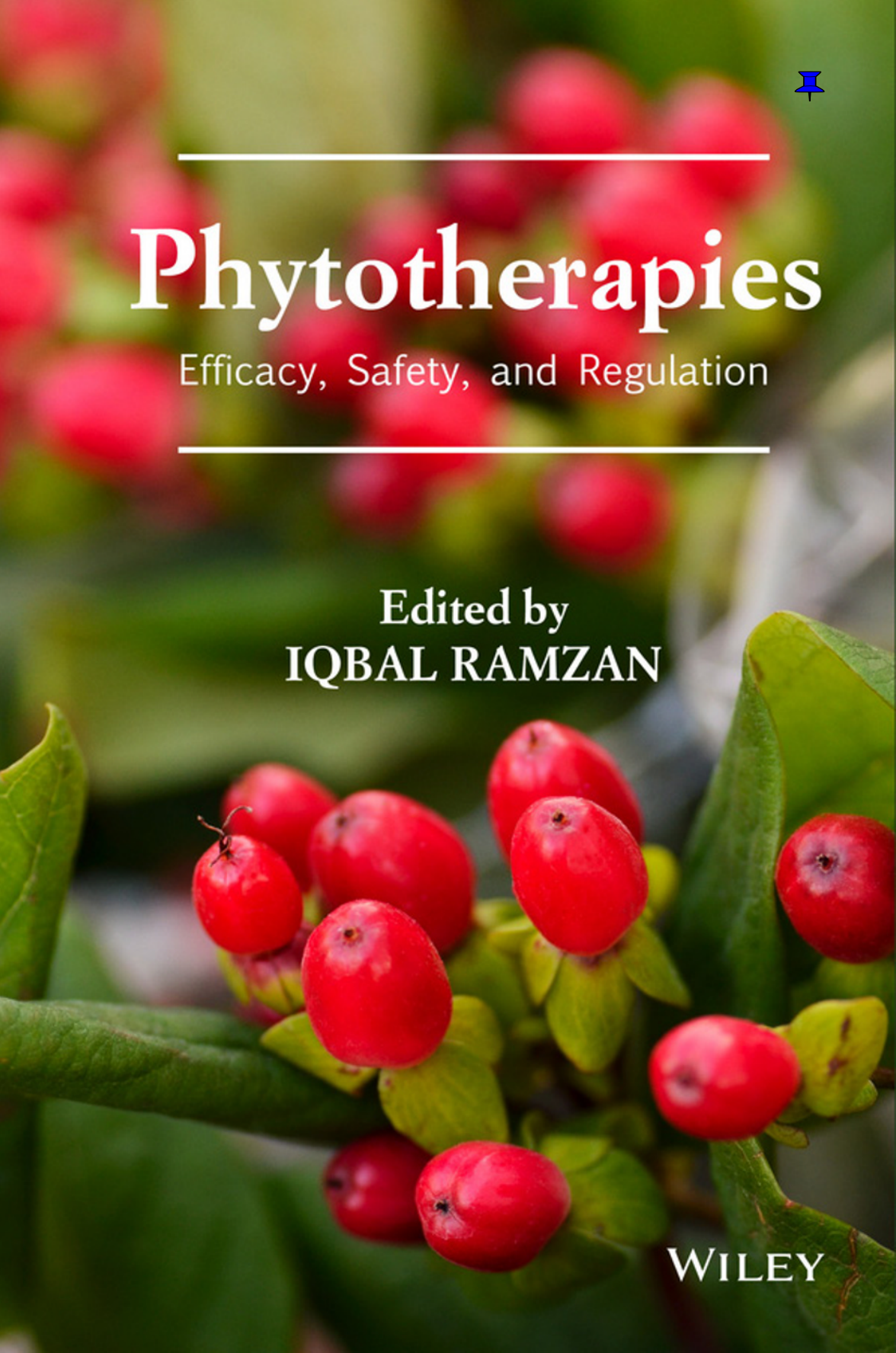
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LIST OF CONTRIBUTORS

Mohi Iqbal Mohammed Abdul, College of Pharmacy, Taibah University, Madina, Kingdom of Saudi Arabia

Bolanle A. Adeniyi, Department of Pharmaceutical Microbiology, University of Ibadan, Ibadan, Nigeria

Maureen V. Boost, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong

Hak-Kim Chan, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Kelvin Chan, Faculty of Pharmacy, The University of Sydney; and National Institute for Complementary Medicine, University of Western Sydney, Sydney, New South Wales, Australia

Meiwan Chen, State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa, Macau, China

Jun-Lae Cho, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Sigrun Chrubasik-Hausmann, Institute of Forensic Medicine, University of Freiburg, Freiburg, Germany

Stephen J. Clarke, Sydney School of Medicine and Northern Clinical School, Kolling Institute of Medical Research, Royal North Shore Hospital, The University of Sydney, Sydney, New South Wales, Australia

Alain Cuerrier, Institut de recherche en biologie végétale, l'Université de Montréal, Montréal, Canada

Pei H. Cui, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Colin C. Duke, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Gabrielle Escalante, Department of Pharmacy Practice, College of Pharmacy, PAHO/WHO Collaborating Center for Traditional Medicine, University of Illinois at Chicago, Chicago, Illinois, USA

Sophia Yui Kau Fong, School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong

Dong Fu, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Qiong Gao, School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong

Cheong Hian Goh, Audit and Licensing Division, Health Products Regulation Group, Health Sciences Authority, Singapore, Republic of Singapore

Paul W. Groundwater, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

David E. Hibbs, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Tom Hsun-Wei Huang, Faculty of Medicine, The University of Sydney, Sydney, New South Wales, Australia

Fangming Jin, School of Pharmacy, Shaanxi University of Chinese Medicine, Xi'an, Shaanxi, China; and Global Therapeutics Pty Ltd, Byron Bay, New South Wales, Australia

Moon-Sun Kim, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Hwee-Ling Koh, Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore, Republic of Singapore

Temitope O. Lawal, Department of Pharmaceutical Microbiology, University of Ibadan, Ibadan, Nigeria

George Q. Li, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Vivian Wan Yu Liao, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Ernest V. Linek, Banner & Witcoff, Ltd., Boston, Massachusetts, USA

Hao Liu, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong

Gail B. Mahady, Department of Pharmacy Practice, College of Pharmacy, PAHO/WHO Collaborating Center for Traditional Medicine, University of Illinois at Chicago, Chicago, Illinois, USA

Laura J. Mahady, The Barrow Neurological Institute and Arizona State University, Phoenix, Arizona, USA

Andrew J. McLachlan, Faculty of Pharmacy and Centre for Education and Research on Ageing, The University of Sydney and Concord Hospital, Sydney, New South Wales, Australia

Pooja Mikkilineni, Department of Pharmacy Practice, College of Pharmacy, PAHO/WHO Collaborating Center for Traditional Medicine, University of Illinois at Chicago, Chicago, Illinois, USA

Rosina Yau Mok, School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong

Christina L. Nance, Department of Pediatrics, Baylor College of Medicine, Immunology, Allergy and Rheumatology, Texas Children's Hospital, Houston, Texas, USA

Rajeshwar Narlawar, School of Chemistry, The University of Sydney, Sydney, New South Wales, Australia

Jennifer A. Ong, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Iqbal Ramzan, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Michel Rapinski, Institut de recherche en biologie végétale, l'Université de Montréal, Montréal, Canada

Michael Rieder, Departments of Paediatrics, Physiology and Pharmacology, and Medicine, Schulich School of Medicine & Dentistry; and Robarts Research Institute, Western University, London, Ontario, Canada

Bashar Saad, Qasemi Research Center-Al-Qasemi Academic College, Baga Algharbiya, Israel; and Faculty of Arts and Sciences, Arab American University Jenin, Jenin, Palestine

Stephen Sagar, Departments of Oncology and Medicine, McMaster University, Hamilton, Ontario, Canada

Susan J. Semple, Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia

Gint Silins, Cullens Patent & Trade Mark Attorneys, Brisbane, Queensland, Australia

Bradley S. Simpson, Flinders Centre for Innovation in Cancer, School of Medicine, Flinders University, Bedford Park, South Australia, Australia

Huanxing Su, State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa, Macau, China

Daniel M.-Y. Sze, School of Medical Sciences and Health Innovations Research Institute (HiRi), RMIT University, Australia

Jennifer Tan, E-TQCM Consultants Limited, Tsuen Wan, Hong Kong

Jian-Bo Wan, State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa, Macau, China

Shengpeng Wang, State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa, Macau, China

Yi-Tao Wang, State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa, Macau, China

Lynn Weekes, NPS MedicineWise, Surry Hills, New South Wales, Australia

Elizabeth M. Williamson, The School of Pharmacy, Whiteknights, Reading, Berkshire, United Kingdom

Raimond Wong, Departments of Oncology and Medicine, McMaster University, Hamilton, Ontario, Canada

Yin Cheong Wong, School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong

Wai-Ping Yau, Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore, Republic of Singapore

Xiao-Jing Zhang, State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Taipa, Macau, China

Qi (Tony) Zhou, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Zhong Zuo, School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong

PREFACE

This book focuses on many facets of the use of Phytotherapies in preventing or treating illness and disease internationally. Phytotherapies are variously defined by practitioners and scientists but include herbal therapies, therapies used by indigenous peoples around the world and alternative medicines as opposed to classical western medicines.

I had not considered editing a book on Phytotherapies as the focus of my scientific career has not been on Phytotherapies. However, in the last 10 years I have investigated some of the pharmacological and more specifically, the hepatotoxic effects of kava. This interest has arisen from my background in that I was born and educated in Fiji where kava is widely used for social and ceremonial functions for centuries.

I was very surprised to receive an invitation from Jonathan Rose at Wiley some 2 years ago to ask if I had an interest in editing such a book. Not having edited an entire book previously, I naively agreed, of course, not realizing the magnitude of the task ahead. I realize now that editing an entire book is exponentially more challenging than contributing to a Book Chapter or even publishing numerous journal articles.

The topic interested me for several other reasons. The Faculty of Pharmacy at the University of Sydney had for many years hosted a Herbal Medicines Education and Research Centre (HMREC) and the Faculty also offered a Masters degree in Herbal Medicines. This program was moderately successful financially and the Centre was closed following an external review that I instituted as Dean of the Faculty. However, I do believe that it is important to examine in a scientific manner, the various forms of Phytotherapies used around the globe as use of such therapies continues to increase.

Phytotherapies are at the heart of disease management in countries such as China and India where they are used instead of and alongside Western medicines.

In the west, the use of Phytotherapies continues to grow at a phenomenal rate. Whether this reflects the dissatisfaction with modern western medicine or the perception that Phytotherapies are natural and thus free of any adverse effects is open to conjecture. However, there is certainly a belief especially among younger people that Phytotherapies are promising alternatives to modern drugs not only in promoting well-being and preventing disease but also in managing some conditions.

Identifying suitable Chapter authors was very challenging due to the diverse and varied nature of the field. I believed it was important to identify suitable scientists with the research and scientific credentials to bring reputational credit to such a book and to ensure balanced and erudite debate. This was confounded by language and cultural sensitivities relating to Phytotherapy use and the evidence base for use in different cultural and ethnic contexts.

Having succeeded in identifying potential Chapter authors the other interesting observation was that while these authors have individually made a strong contribution to the evidence base for the use of Phytotherapies some were also philosophically committed to clinical paradigms that promote the use of Phytotherapies. Separating this attachment to the adoption of Phytotherapies from the scientific evidence for their use was an additional challenge that I had not anticipated in accepting to edit such a book.

If you, the reader, like this book and find it informative and useful in either your practice, for your students or indeed as a resource in your scientific library, then I hope I have been able to objectively separate out the evidence base and summarise some of the science in this vast field of Phytotherapies. The other issue which I wanted to come across in the book is the rightful acknowledgment of the breath of the topic and the variety of the evidence base that is available for the use of Phytotherapies.

I want to thank Angela Teklic for her tireless effort in assisting me with the formatting of the Chapters and making sure that the Book complied with the Wiley template. Both of us underestimated this mammoth task but the attention to detail displayed by Angela made my life more bearable. Eleanor Luntao was very valuable in making sure the contributor agreements were in place and that permissions to reproduce published material were obtained. Eleanor's dedication during the proof-reading stage was also exemplary. Finally, I would like to thank my wife, Dr Lynn Weekes AM, who had to spend many hours alone while I spent days editing this book.

Professor IQBAL RAMZAN

The University of Sydney
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PHYTOTHERAPIES—PAST, PRESENT, AND FUTURE

Iqbal Ramzan and George Q. Li
Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

1.1 OVERVIEW OF PHYTOTHERAPY

1.1.1 Definition

Phytotherapy, or the use of herbal medicines to prevent or treat a disease, is a traditional medical practice based on medicinal plants. It is a branch of complementary and alternative medicine (CAM) or traditional medicine, which refers to traditional medicine systems and various forms of Indigenous medicine [1]. Many different cultures have developed herbal medicine systems, for example, Western herbal medicines, Chinese herbal medicines, Ayurvedic and Unani medicines, and Australian Indigenous medicines [2]. Phytotherapy is the basis of modern pharmaceutical science, with about 25% of the drugs prescribed today, such as digoxin, aspirin, and paclitaxel being derived from plants [3].

Western herbal medicine and orthodox medicine share to a large degree a common physiologic and diagnostic system, but they are different in many important ways as well. Herbs are complex mixtures of chemicals, which may have several distinct and concurrent pharmacological activities, while pharmaceutical drugs are mostly single chemical entities. Modern herbal medicines are becoming part of integrative clinical management in medical textbooks as exemplified in *Natural Standard Herbal Pharmacotherapy* [4].

Traditional Chinese Medicine (TCM) is another popular traditional medical system in China and worldwide. It includes various practices including Chinese

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herbal medicine, acupuncture, and massage, sharing a fundamental principle that the human body is part of the whole universe. The treatment goals are harmonization and balance using a holistic approach. The basic theories of TCM are Yin and Yang theory, Five-Element theory, Zang Fu (viscera and bowels) theory, Meridian, Qi, Blood and Fluid theory, Syndrome Differentiation, and Treatment theory. Detailed information on TCM can be found in textbooks on Chinese medicine [5–8]. For example, the blockage by Phlegm is closely related to excessive fat retention in metabolic syndrome and the management with herbal formulations and other modalities is to eliminate the Phlegm [9]. Treatment of diabetes with TCM focuses on nourishing Yin, clearing Heat, producing Body Fluid, and moistening Dryness using herbal formulae composed of herbs such as Rehmannia (*Rehmannia glutinosa*) and yam (*Dioscorea opposita*) [10].

Modernization of TCM and integration with orthodox medicine and science is a model accepted in China, covering education, clinical practice, and research. Modern pharmacologic and clinical studies have been used to examine claims of traditional practice; chemistry and chemical analysis are used for quality control of Chinese herbal medicines. Pharmacological and chemical studies have revealed connections between nature of herbal medicines and pharmacological activities, herbal tastes, and chemical components. For example, ephedra is warm as it contains ephedrine, a sympathomimetic amine; pungent herbs contain essential oils; sour herbs contain acid and tannins; sweet herbs contain sugars, proteins, and amino acids; bitter herbs contain alkaloids and glycosides; and salty herbs contain inorganic salts. Pharmacokinetic studies demonstrate a link between the tissue distribution of active chemical constituents and the attributive meridians of Chinese herbal medicines.

The World Health Organization (WHO) has a long-term interest in promoting traditional medicines and has produced a series of publications on global atlas [11], good agricultural practices [12], and monographs on selected medicinal plants [13], providing scientific information on the safety, efficacy, and quality control of widely used medicinal plants. The latest version of *WHO Traditional Medicine Strategy* (2014–2023) was developed to support Member States in harnessing the potential contribution of traditional medicine to health, wellness, and health care; and promoting the safe and effective use of traditional medicines by regulating, researching, and integrating traditional medicine products, practitioners, and practice into health systems [14].

1.1.2 International Trend in the Usage of Complementary Medicines

Complementary medicines have maintained their popularity in all regions of the world. The global market for herbal medicines is significant and growing rapidly. In China, traditional herbal preparations account for approximately 40% of the total health care delivered [1]. In the United States, over 42% of the population have used complementary or alternative medicine at least once. Total out-of-pocket expenditure relating to alternative therapies in 1997 was conservatively estimated at $27.0 billion, which is comparable with the projected 1997 out-of-pocket expenditure for all US

physician services [15]. In the United Kingdom, estimate of annual out-of-pocket expenditure on practitioner visits in 1998 was £450 million [16].

In Australia, it has been reported that in 2000, 52% of the population used at least one nonmedically prescribed complementary medicine [17]. The estimated expense on complementary medicines was nearly twice the patient expenditure on pharmaceutical medicines during 1992–1993 [17]. The expenditure on alternative therapies in 2000 was $AUD 2.3 billion [18]. In 2005, the annual out-of-pocket expenditure was estimated to be $AUD 4.13 billion [19]. More recent studies have indicated that complementary medicines are finding a growing preference amongst patients with chronic or serious diseases who are looking for natural options to assist in the ongoing management of these conditions. For instance, St. John's wort preparations have low rates of side effects and good compliance, comparatively low cost, making it worthy of consideration in the management of mild-to-moderate depression [20]. An overview of complementary medicines use and regulation in Australia is available in the Australian government's commissioned report, *Complementary Medicines in the Australian Health System* [21].

1.2 PRECLINICAL RESEARCH ON PHYTOTHERAPIES

1.2.1 Pharmacognosy and Quality Standardization of Phytotherapies

Pharmacognosy is the study of medicinal materials, mainly plants, using theory and methods of modern sciences such as botany, zoology, chemistry, pharmacology, and traditional medicines to study the origin, production, harvesting and processing, identification and evaluation, chemical components, physical and chemical properties, resource development, pharmacology, toxicology, and therapeutic application of herbal medicines to ensure the quality of herbal materials and to develop new herbal resources. Its main focus is on the study of authentication and quality control of herbs [22].

Plant descriptions are used in the identification of herbal materials. They are first classified by the plant parts of origin, such as roots and rhizomes, stems, leaves, flowers, fruits, or whole herbs. Then the macroscopic and microscopic descriptions are included in each monograph. Some microscopic features reflect the secondary metabolites, starch granules, resin ducts, and oil cells. The macroscopic features are still very useful for authentication; for example, the colors of herbs such as yellow coptis, brown rhubarb, and black valerian are related to their alkaloid, anthraquinone, and iridoid contents, respectively.

Pharmacognosy, particularly correct identification and high quality of the herb, is the foundation of safety, clinical efficacy, and research on phytotherapy. It is a subject most relevant to professionals in testing laboratories, herbal dispensing, and regulatory bodies. Pharmacognosy is the principal discipline employed in national and international pharmacopeia in the form of the following topics: species identification using plant taxonomy, macroscopic identification using morphology, microscopic identification using anatomy, and quality control with analytical

methods. The WHO monographs are examples of such comprehensive monographs [13], while *British Pharmacopoeia* used as statutory standards in Europe and Australia focuses on chemical analysis for quality control [23].

Bioequivalence is a useful concept in the quality standardization of herbal medicines. *European Guideline on the Investigation of Bioequivalence* defined bioequivalence as same active substances and similar bioavailability that results in similar clinical effectiveness and safety [24]. To approve two products to be bioequivalent, the following studies need to be carried out: pharmaceutical equivalence (quality standardization), pharmacokinetic equivalence (same bioavailability and time-to-peak concentration), pharmacodynamic equivalence (*in vivo* and *in vitro*), and therapeutic equivalence (clinical study). For example, a study found that the bioavailability of ginkgolide A, ginkgolide B, and bilobalide of two different *Ginkgo biloba* commercial brands were clearly different and did not demonstrate bioequivalence of test and reference products. The slow *in vitro* dissolution of the test product resulted in a large decrease in bioavailability [25]. The bioequivalence concept implies the need for a comprehensive platform for evaluation of herbal products [22].

Kudzu root is an example of a herb requiring a comprehensive quality control platform. Kudzu is one of the most commonly used Chinese herbal medicines for the treatment of diabetes, cardiovascular disease, and many other conditions. It includes two closely related species, *Pueraria lobata* and *Pueraria thomsonii*, which are not well-differentiated in pharmacopoeias. Isoflavonone puerarin is currently used as a marker for quality control of the species [26]. Recent studies indicate that ultra-performance liquid chromatography combined with partial least square discriminant analysis (PLS-DA) was more effective than using puerarin alone in differentiating the two species [27]. HPTLC coupled with multivariate classification analyses has also been used effectively to differentiate the two species [28].

Similarly, multiple markers have been used in the quality control of propolis. High-performance liquid chromatography with UV detection has been used to simultaneously quantify the eight major bioactive phenolic compounds in Chinese propolis [29] and a rapid thin-layer chromatography combined with chemometric fingerprinting has also been used to distinguish Chinese propolis from poplar tree gum [30].

1.2.2 Pharmacological Studies and Identification of Bioactive Compounds

Herbal pharmacology is the study of the function and mechanism of action of herbal medicines in biological systems and the pharmacokinetics of herbal compounds with modern scientific methods to understand the underlying nature of the likely clinical application. Herbal medicines are unique in that they contain multiple components and can act on multiple pharmacologic targets. The major types of herbal pharmacology research are *in vitro* studies at the cellular or tissue level to uncover the mechanism of action of the herbal components at the molecular level, for example, cytotoxicity in cancer cell lines; whole animal models to test preclinical properties of herbal medicines and to determine the pharmacokinetic properties, for example, streptozotocin-induced diabetic rats and human clinical studies to confirm the efficacy and safety of the herbal medicines. For instance, preclinical and limited clinical

evidence have shown pentacyclic triterpenoids including the oleanane, ursane, and lupane groups have multiple biological activities and may contribute to their use in traditional medicine for the treatment of diabetes and diabetic complications [31]. Increasing evidence also has shown common chemical components such as gallic acid, a common phenolic compound, playing some role in the potential health benefits of food and nutraceuticals [32, 33]. Quercetin is clinically used as a nutraceutical for cardiovascular disease [34], and berberine has been used for the management of diabetes [35].

St. John's wort is an example of a herb with a huge body of research on the chemistry, analysis, and pharmacological actions. The active compounds may include naphthodianthrones (e.g., hypericins), flavonoids (rutin, quercetin), and phloroglucinols (hyperforin) individually or in combination. St. John's wort extracts have been found to interact with a number of neurotransmitter systems implicated in depression and in psychiatric illness generally, such as uptake of serotonin, noradrenaline, and dopamine and to interact with γ-aminobutyric acid (GABA) receptors, monoamine oxidases, catechol-*O*-methyltransferase, and dopamine-beta hydroxylase [36]. However, the exact active compound(s) and mechanism(s) are still to be fully defined.

Lavender flower (*Lavandula officinalis*) is another example of a herb having multiple actions. This herb is used for anxiety, insomnia, antimicrobial activity, dyspepsia, wounds, and sores, and pharmacological studies have focused on anxiety, but cover other actions. Lavender oil showed significant dose-dependent anxiolytic activity in rats and mice, comparable to that of the standard anxiolytic agent lorazepam and also increased pentobarbital-induced sleeping time [37]; lavender oil also lowered the mean heart rate in dogs [38]. Mechanistic studies revealed it inhibited voltage-dependent calcium channels in synaptosomes, primary hippocampal neurons [39], and increased the dopamine D3 receptor subtype in the olfactory bulb of mice [40]. The lavender essential oils are dominated by oxygenated monoterpenes including linalyl acetate, linalool, 1,8-cineole, fenchone, camphor, nerol, and borneol. However, the exact compositions are dependent on the varieties and steaming process [38, 41, 42], which can impact the biological and clinical outcomes. While the current actions are mostly based on the total effects of the essential oils, identification of active ingredients should help future quality standardization of the extracts.

Overall, for most herbal medicines, the mechanism of action and the nature of active constituents are still not well-defined. Furthermore, most research involving herbal medicines concentrates on establishing biological activities of purified single compounds, or crude extracts without a defined fingerprint of the extract or formulation. New research platforms need to be multidisciplinary in nature to cover the research from single constituent activity to multiple biological activities linking to various standardized extracts.

1.2.3 Application of Proteomics and Metabolomics in Phytotherapy Research

To address the multi-ingredient and multitarget nature of herbal medicines and TCM formulae, network pharmacology or systems biology approach has been used in phytotherapy research in the past few years [43, 44]. Protein–protein interaction

network and topological attributes related to the biological targets of the ingredients were integrated to identify active ingredients in herbal medicines [45].

Progress in analytical techniques, such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) combined with bioinformatics, proteomics, and metabolomics have attracted increasing attention. The use of metabolomics has led to the discovery of the metabolite 2-aminoadipic acid as a marker of diabetes risk in humans [46] and two differentiating urinary metabolites involved in key metabolic pathways of sugar have been identified in high-fat-diet-induced type 2 diabetic rats [47].

Proteins and small metabolites are more responsive to disease, environment, and drug treatment and may be more relevant to the holistic approach in traditional medicines [48, 49]. Omic studies may provide answers on epigenetic effects on gene expression and polymorphisms of cytochrome P450 liver enzymes or P-glycoprotein [50]. Herbal medicines have elicited changes in proteins in wound healing in rats [51] and liver HepG2 cells [52]. Treatment with berberine of patients with type 2 diabetes and dyslipidemia led to a highly significant decrease in the concentrations of 13 fatty acids, suggesting that berberine might play a pivotal role in the treatment of type 2 diabetes by downregulating the high level of free fatty acids [35]. In rats, epimedium herb was shown to reverse perturbations in plasma levels of phenylalanine, tryptophan, cholic acid, and other metabolites regulating oxidant–antioxidant balance, amino acid, lipid, and energy metabolism, respectively, and gut microflora [53].

1.3 CLINICAL RESEARCH ON PHYTOTHERAPIES

1.3.1 Efficacy of Popular Phytotherapies

Clinical evidence on herbal medicine comes as case reports and/or clinical data. In the past 5 years, there have been over two hundred systematic reviews on herbal medicines and traditional Chinese medicines published in the Cochrane Library, including reviews on the most popular herbs, such as ginkgo (*Ginkgo biloba*), St. John's wort (*Hypericum perforatum*), ginseng (*Panax ginseng*), valerian (*Valeriana officinalis*), hawthorn (*Crataegus monogyna*), echinacea (*Echinacea* species), milk thistle (*Silybum marianum*), bitter melon (*Momordica charantia*), and black cohosh (*Cimicifuga* species).

Although a large number of trials report positive outcomes, the reviews reveal no conclusive evidence on the efficacy of the popular herbs, including ginkgo for cognitive impairment and dementia [54], ginseng for cognition [55], echinacea for preventing and treating the common cold [56], milk thistle for alcohol or nonalcohol hepatitis and other liver diseases [57], bitter melon for type 2 diabetes mellitus [58], and black cohosh and phytoestrogens for menopausal symptoms [59, 60]. A positive conclusion has been drawn for St. John's wort for major depression, as available evidence suggests that the hypericum extracts tested in the relevant trials are superior to placebo in patients with major depression; and are as effective as standard antidepressants [61]. In addition, hawthorn extract is beneficial in symptom control as an adjunct for chronic heart failure treatment [62].