



Phytotherapies

Efficacy, Safety, and Regulation

Edited by
IQBAL RAMZAN

WILEY

PHYTOTHERAPIES

PHYTOTHERAPIES

Efficacy, Safety, and Regulation

Edited by

IQBAL RAMZAN

WILEY

Copyright © 2015 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permissions>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Phytotherapies : efficacy, safety, and regulation / edited by Iqbal Ramzan.
p. ; cm.

Includes bibliographical references and index.

ISBN 978-1-118-26806-3 (cloth)

I. Ramzan, Iqbal, 1951–, editor.

[DNLM: 1. Phytotherapy–methods. 2. Phytotherapy–standards.

3. Quality Assurance, Health Care. WB 925]

RS164

615.321–dc23

2014049520

Set in 10/12pt Times LT Std by SPi Global, Pondicherry, India

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

1 2015

CONTENTS

List of Contributors	xvii
Preface	xxi
1 Phytotherapies—Past, Present, and Future	1
<i>Iqbal Ramzan and George Q. Li</i>	
1.1 Overview of Phytotherapy	1
1.1.1 Definition	1
1.1.2 International Trend in the Usage of Complementary Medicines	2
1.2 Preclinical Research on Phytotherapies	3
1.2.1 Pharmacognosy and Quality Standardization of Phytotherapies	3
1.2.2 Pharmacological Studies and Identification of Bioactive Compounds	4
1.2.3 Application of Proteomics and Metabolomics in Phytotherapy Research	5
1.3 Clinical Research on Phytotherapies	6
1.3.1 Efficacy of Popular Phytotherapies	6
1.3.2 Chinese Herbal Medicines	7
1.3.3 Food Nutrition and Translational Research	7
1.4 Safety of Phytotherapies	8
1.5 Profile of Research in Complementary Medicine	9
1.5.1 International Profile	9
1.5.2 Australian Profile of Research in Complementary Medicines	10
1.6 Summary and Future Directions	12
References	12

2	Quality Control and Quality Assurance of Phytomedicines: Key Considerations, Methods, and Analytical Challenges	18
	<i>Wai-Ping Yau, Cheong Hian Goh, and Hwee-Ling Koh</i>	
2.1	Introduction	18
2.2	Key Considerations in QC/QA of Phytomedicines	20
2.2.1	Identification and Good Agricultural and Collection Practices (GACP)	20
2.2.2	Contamination	22
2.2.3	Substitution	25
2.2.4	Adulteration	25
2.2.5	Contents and Standardization	26
2.2.6	Stability	26
2.2.7	Processing	26
2.3	Methods for QC/QA of Phytomedicines	27
2.3.1	Macroscopic Evaluation	27
2.3.2	Microscopic Evaluation	27
2.3.3	Physicochemical Analysis	29
2.3.4	Chemical Fingerprinting	29
2.3.5	DNA Fingerprinting	35
2.3.6	“Omics” Technology	36
2.4	Challenges	37
2.5	Conclusions	40
	References	40
3	Preclinical (<i>In Vivo</i>) and Laboratory (<i>In Vitro</i>) Evidence of Phytomedicine Efficacy	49
	<i>Mohi Iqbal Mohammed Abdul and Tom Hsun-Wei Huang</i>	
3.1	Introduction to Development of Drugs from Nature	49
3.2	Use of <i>In Vitro</i> and <i>In Vivo</i> Models in Herb Drug Research: Learning Thus Far	50
3.2.1	<i>In Vitro</i> Assays	50
3.2.2	<i>In Vivo</i> Assays	51
3.3	Cardiovascular- and Stroke-Related Diseases: <i>In Vitro</i> and <i>In Vivo</i> Focus	53
3.3.1	Cardiovascular Diseases	53
3.3.2	Stroke	55
3.4	Conclusions	60
	References	61
4	Clinical Efficacy Trials with Natural Products and Herbal Medicines	65
	<i>Christina L. Nance</i>	
4.1	Introduction	65
4.2	Trials in Various Disease States	66

4.2.1	Profile: RCT of Natural Product in Rheumatoid Arthritis (RA)	66
4.2.2	Asthma	67
4.2.3	Cancer	68
4.2.4	Cardiovascular Disease	68
4.2.5	Diabetes	69
4.2.6	Dermatology	70
4.2.7	Gastroenterology	70
4.2.8	Viral Infections	72
4.3	Natural Product: Green Tea	73
4.3.1	Green Tea Catechin, Epigallocatechin Gallate (EGCG)	73
4.4	EGCG Clinical Trials	75
4.4.1	Polyphenon E	75
4.4.2	Safety, Toxicity, and Pharmacokinetics	75
4.4.3	Metabolism	76
4.4.4	Clinical Studies	76
4.4.5	Cancer Studies	77
4.5	Human Clinical Study: EGCG and HIV-1 Infection	78
4.5.1	Translational Medicine: EGCG: Bench-to-Bedside	78
4.5.2	Phase I Clinical Trial: Polyphenon E in HIV-1 Infection	79
4.6	Conclusion	80
	References	80
5	Novel Formulations and Drug Delivery Systems for Phytotherapies	89
	<i>Shengpeng Wang, Meiwan Chen, Qi (Tony) Zhou, and Hak-Kim Chan</i>	
5.1	Limitations of Conventional Formulations for Herbal Medicines	89
5.1.1	Barriers in Physicochemical and Biological Properties	89
5.1.2	Challenges in Quality and Safety Assurance	90
5.1.3	Conventional Formulations Limit the Therapeutic Efficacy of Herbal Medicines	90
5.2	Crucial Issues of Developing Novel Delivery Systems for Herbal Medicines	91
5.2.1	How Novel Delivery Systems Follow the Tradition?	91
5.2.2	Pharmacokinetic Research on Delivery Systems for Herbal Medicines	92
5.2.3	Safety Considerations on Delivery Systems for Herbal Medicines	92
5.3	Novel Delivery Systems of Herbal Medicines	93
5.3.1	Pulmonary Delivery of Herbal Medicines	93
5.3.2	Nanocarriers of Herbal Medicines for Drug/Gene Delivery	94
5.3.3	Surface Modification of Nanocarriers by Herbal Medicines	95
5.3.4	Herbal Medicines as Photosensitizers for Photodynamic Therapy	95
5.4	Summary	96
	References	97

6	Phytotherapies Used by Indigenous Populations	101
	<i>Bradley S. Simpson and Susan J. Semple</i>	
6.1	Introduction	101
6.2	Phytotherapies of Indigenous Australians	103
6.2.1	Introduction	103
6.2.2	Philosophy and Knowledge Transmission	104
6.2.3	Ailments Treated with Medicinal Plants	106
6.2.4	How Plant Medicines Have Been Used	107
6.2.5	Methods of Plant Preparation	109
6.2.6	Prized and Commonly Used Plants in Australian Indigenous Medicine	111
6.3	Challenges of a Changing Environment	114
6.3.1	Safety of Australian Phytotherapies	115
6.3.2	Development and Regulation of Australian Indigenous Medicines	116
6.3.3	Integration of Traditional and Western Medicine in Indigenous Populations	117
6.4	Conclusions	117
	References	118
7	Phytotherapies from Traditional Chinese Medicine	122
	<i>Michael Rieder</i>	
7.1	Traditional Chinese Medicine	122
7.2	Key Concepts in Traditional Chinese Medicine	124
7.3	Herbal Medicine and Traditional Chinese Medicine	126
7.4	Issues in the Development of Phytotherapy from Traditional Chinese Medicine	130
7.5	Phytotherapies Developed from Traditional Chinese Medicine	131
7.6	Huang Qin Tang and the Development of PHY906	134
7.7	Ginseng	136
7.8	Moving Forward	138
	References	138
8	Integrating Traditional Greco-Arab and Islamic Diet and Herbal Medicines in Research and Clinical Practice	142
	<i>Bashar Saad</i>	
8.1	Introduction	142
8.2	Food Therapy in Greco-Arab and Islamic Medicine	147
8.2.1	Honey	148
8.2.2	Olive Oil	149
8.2.3	Dates	151
8.2.4	Carob (<i>Ceratonia siliqua</i>)	152
8.2.5	Fig (<i>Ficus carica</i>)	153
8.2.6	Pomegranate (<i>Punica granatum</i>)	153
8.2.7	Garlic (<i>Allium sativum</i>) and Onion (<i>Allium cepa</i>)	154

8.2.8	Edible Wild Plants	154
8.3	Medicinal Plants	157
8.3.1	Black Seed (<i>Nigella sativa</i>)	160
8.3.2	Fenugreek (<i>Trigonella foenum-graecum</i>)	167
8.3.3	Sage (<i>Salvia officinalis</i>)	168
8.3.4	Khella (<i>Ammi visnaga</i>)	168
8.3.5	Milk Thistle (<i>Silybum marianum</i>)	168
8.3.6	Marjoram (<i>Origanum majorana</i>)	171
8.3.7	Garlic (<i>Allium sativum</i>) and Onion (<i>Allium cepa</i>)	172
8.3.8	Tayun (<i>Inula viscose</i>)	172
8.3.9	Rocket (<i>Eruca sativa</i>)	172
8.3.10	Nettle (<i>Urtica dioica</i>)	173
8.3.11	Peppermint (<i>Mentha piperita</i>)	173
8.3.12	Chamomile (<i>Chamomilla recutita</i>)	174
8.3.13	Coriander (<i>Coriandrum sativum</i>)	175
8.3.14	Anise (<i>Pimpinella anisum</i>)	175
8.3.15	Rosemary (<i>Rosmarinus officinalis</i>)	175
8.3.16	Devil's Dung (<i>Ferula asafetida</i>)	176
8.3.17	Ginger (<i>Zingiber officinale</i>)	176
	References	177
9	Evolution of Herbal Medicines in Europe and its Relationship with Modern Medicine	183
	<i>Elizabeth M. Williamson and Kelvin Chan</i>	
9.1	Background	183
9.2	Historical Perspective	184
9.3	European Herbal Medicine: Relationship with Modern Medicine	194
9.4	Summary	194
	References	196
10	Chemical Classification and Chemistry of Phytotherapeutics Constituents	199
	<i>Pei H. Cui and Colin C. Duke</i>	
10.1	Introduction	199
10.2	Phytochemicals	201
10.2.1	Alkaloids	201
10.2.2	Flavonoids	205
10.2.3	Glycosides and Saponins	208
10.2.4	Phytosterols	209
10.2.5	Fatty Acids	212
10.2.6	Essential Oils	214
10.2.7	Terpenes	214
10.3	Other Phytochemicals	215
10.4	Medicinal Effects Relating to Dietary Intake	217

10.4.1	Anti-oxidants	217
10.4.2	Omega-3 Long Chain Fatty Acids and Derivatives	220
10.5	Natural Products as Leads for Drug Development	223
10.5.1	Catechol Moiety of Piceatannol: Implication and Significance	224
10.5.2	SAR Studies for Drug Development	226
10.6	Summary	230
	References	230
11	Therapeutic Potential of Ginsenosides in Management of Atherosclerosis	236
	<i>Xiao-Jing Zhang, Huanxing Su, Yi-Tao Wang, and Jian-Bo Wan</i>	
11.1	Introduction	236
11.2	Chemical Diversity of Ginsenosides and Distribution	238
11.3	Anti-Atherosclerotic Effects of Ginsenosides	240
11.4	Underlying Mechanisms of Ginsenosides Against Atherosclerosis	244
11.4.1	Regulation of Blood Lipid Profile	244
11.4.2	Anti-oxidant Activity	251
11.4.3	Anti-vascular Inflammation	252
11.4.4	Effect on Vascular Cells	255
11.4.5	Anti-platelet Effects	257
11.4.6	Anti-angiogenesis Effects	257
11.5	Conclusions and Future Perspectives	258
	Acknowledgments	258
	References	258
12	Phytotherapy Pharmacophores for Major Cellular Drug Targets	268
	<i>Jennifer A. Ong, Paul W. Groundwater, and David E. Hibbs</i>	
12.1	Introduction	268
12.2	What is a Pharmacophore?	269
12.3	Pharmacophore Models of Cardiovascular Drugs	270
12.4	Pharmacophore Models for Anticancer Drugs	285
12.5	Pharmacophore Models for Anti-Inflammatory Drugs	290
12.6	Pharmacophore Models for Anti-Infective Drugs	297
12.7	Pharmacophore Models for Neurological Drugs	299
12.8	Pharmacophore Models for Miscellaneous Drugs	305
12.9	Conclusions	309
	References	309

13 Use of Kava as a Phytotherapeutic Agent and Kava-Related Hepatotoxicity	312
<i>Dong Fu and Iqbal Ramzan</i>	
13.1 Introduction	312
13.2 Active Components in Kava	313
13.3 Therapeutic Applications of Kava	314
13.4 Pharmacology of Kava	314
13.4.1 Anti-psychotic Effects of Kava	314
13.4.2 Anti-cancer Effects of Kava	316
13.5 Side Effects of Kava	317
13.6 Hepatotoxicity of Kava	318
13.6.1 Inhibition of Cytochrome P450 Enzymes Activities	318
13.6.2 Reduction of Liver Glutathione	319
13.6.3 Induction of Hepatic Inflammatory Responses	320
13.6.4 Inhibition of Cyclooxygenase Enzyme Activity	320
13.6.5 Inhibition of Hepatic Transporters	321
13.6.6 Damage of Hepatic Mitochondria	321
13.7 Summary and Future Challenges	322
References	323
14 Phytotherapies as New Drug Sources: Gossypol and Curcumin	330
<i>Vivian Wan Yu Liao, Rajeshwar Narlawar, David E. Hibbs, and Paul W. Groundwater</i>	
14.1 Botanical Sources of Gossypol and Curcumin	330
14.2 Stereoisomerism, Tautomerism, and Reactivity	332
14.2.1 Stereoisomerism	332
14.2.2 Tautomerism	333
14.2.3 Reactivity	333
14.3 Biological Activity of Gossypol and its Analogues	337
14.3.1 Antifertility	337
14.3.2 Anticancer	338
14.3.3 Antiviral	341
14.3.4 Antimalarial	345
14.3.5 Other Biological Activity	346
14.4 Biological Activity of Curcumin and its Analogues	346
14.4.1 Introduction	346
14.4.2 Anticancer	348
14.4.3 Anti-inflammatory and Antioxidant	354
14.4.4 Curcumin in Neurodegenerative Diseases	357
14.4.5 Antimalarial	359
14.4.6 Other Biological Activity	360
References	360

15	Phytotherapies for the Management of Obesity and Diabetes	370
	<i>Michel Rapinski and Alain Cuerrier</i>	
15.1	Introduction	370
15.2	Plants from the North American Pharmacopoeia	372
15.3	Pharmacological Screening: Providing Empirical Evidence for Phytotherapies	379
15.3.1	Diabetes	379
15.3.2	Obesity	384
15.4	Community-Based Participation: Developing Phytotherapies from Traditional Knowledge	385
15.5	Conclusions	387
	References	387
16	Phytotherapeutics for Cancer Therapy	394
	<i>Daniel M.-Y. Sze, Hao Liu, Maureen V. Boost, Raimond Wong, and Stephen Sagar</i>	
16.1	Introduction	394
16.2	Anticancer Phytotherapeutics With NK Enhancement	395
16.2.1	Effects of Clinically Useful Phytocompounds on Cancer Patients' NK Cell Immunity, Quality of Life (QoL), and Overall Survival	395
16.2.2	Commonly Used Phytotherapeutics in Cancer Management	395
16.2.3	Phytotherapeutic Formulae for Cancer via NK Modulation	409
16.3	Conclusions	423
	References	425
17	Phytomedicines for Fatty Liver Disease and Functional Gastrointestinal Conditions	429
	<i>George Q. Li, Moon-Sun Kim, Fangming Jin, and Jun-Lae Cho</i>	
17.1	Introduction	429
17.2	Phytomedicines for FLD	430
17.2.1	Introduction and Pharmacotherapy	430
17.2.2	Treatment of Fatty Liver with Herbal Medicines	433
17.2.3	Common Herbs Used in Fatty Liver Management	433
17.3	Phytomedicines for IBS	439
17.3.1	Introduction and Pharmacotherapy	439
17.3.2	Treatment of IBS in Traditional Medicine	440
17.3.3	Common Herbs Used in the Management of IBS	440
17.4	Phytomedicines for Constipation	444
17.4.1	Treatment of Constipation with Herbal Medicines	445

17.4.2	Common Herbs Used in the Management of Constipation	446
17.5	Summary and Future Perspectives	448
	References	448
18	Phytopharmaceuticals for Inflammatory Conditions	464
	<i>Sigrun Chrubasik-Hausmann</i>	
18.1	Traditional Medicines for Inflammatory Conditions in Europe	464
18.2	Twenty-First-Century Update on PAIDs	465
18.3	Oral Extracts from <i>Salix</i> Species	465
18.3.1	Efficacy	467
18.3.2	Safety	467
18.4	Oral Extracts from <i>Harpagophytum Procumbens</i>	468
18.4.1	Efficacy	469
18.4.2	Safety	469
18.5	Oral Avocado–Soybean Unsaponifiables	469
18.5.1	Efficacy	470
18.5.2	Safety	473
18.6	Oral Extracts From <i>Tripterygium wilfordii</i>	473
18.6.1	Efficacy	473
18.6.2	Safety	474
18.7	Oral PAIDs Containing Unsaturated Fatty Acids	475
18.7.1	Efficacy	475
18.7.2	Safety	475
18.8	Other Oral PAIDs	476
18.9	Topical PAIDs	477
18.9.1	Efficacy	478
18.9.2	Safety	478
	References	478
19	Phytotherapies for Infectious Diseases: Are These Really Useful?	483
	<i>Gail B. Mahady, Gabrielle Escalante, Pooja Mikkilineni, Laura J. Mahady, Temitope O. Lawal, and Bolanle A. Adeniyi</i>	
	The History of Medicine	483
19.1	Introduction	484
19.2	Historical Precedent for Natural Products as Antimicrobial Drugs	486
19.3	Are Phytotherapies Useful for the Treatment of Infectious Diseases?	487
19.3.1	Cranberry (<i>Vaccinium macrocarpon</i> Ait)	488
19.3.2	Turmeric (<i>Curcuma longa</i> L.) as an Antimicrobial Agent	492
19.3.3	Ginger (<i>Zingiber officinale</i> L.) as an Antimicrobial Agent	494
19.4	Naturally Occurring Compounds that may Reduce Zoonosis	495
19.5	Synergistic and Additive Effects with Antibiotics	496
19.6	New Emerging Infectious Diseases and those with no Known Treatments	496

19.7	SARS	497
19.8	Reducing MRSA Carriage	498
19.9	Conclusions	499
	References	500
20	Phyto medicines for CNS Disorders: Safety Issues for use with Antiepileptic Drugs	504
	<i>Sophia Yui Kau Fong, Rosina Yau Mok, Qiong Gao, Yin Cheong Wong, and Zhong Zuo</i>	
20.1	Introduction	504
20.2	Methodology of Systematic Literature Search	506
20.3	Pharmacokinetic Interactions	506
20.3.1	Carbamazepine	507
20.3.2	Phenytoin	507
20.3.3	Valproate	510
20.3.4	Diazepam	511
20.3.5	Phenobarbitone	511
20.3.6	Newer Generations of Antiepileptic Drugs	512
20.4	Pharmacodynamic Interactions	512
20.4.1	Antiepileptic Effects	513
20.4.2	Sedative Effects	517
20.4.3	Anxiolytic Effects	520
20.4.4	Memory Impairment Effects	520
20.4.5	Motor Incoordination Effects	523
20.5	Conclusions	524
	References	524
21	Phytotherapies: Drug Interactions in Cancer	536
	<i>Andrew J. McLachlan and Stephen J. Clarke</i>	
21.1	Introduction	536
21.2	Use of Herbal and Complementary Medicines by People Living with Cancer	537
21.3	Mechanisms of Phytotherapy–Drug Interactions	538
21.4	Selected Examples of Phytotherapy Medicines that have the Potential to Cause Drug Interactions in Cancer	540
21.4.1	Black Cohosh (<i>Cimicifuga racemosa</i>)	540
21.4.2	Echinacea (<i>Echinacea purpurea</i>)	541
21.4.3	Fenugreek (<i>Trigonella foenum graecum</i>)	541
21.4.4	Ginkgo Biloba	542
21.4.5	Asian Ginseng (<i>Panax ginseng</i>)	542
21.4.6	Green Tea (<i>Camellia sinensis</i>)	543
21.4.7	Kava Kava (<i>Piper methysticum</i> Forst. f.)	544
21.4.8	Liquorice (<i>Glycyrrhiza uralensis</i>)	544
21.4.9	Milk Thistle (<i>Silybum marianum</i>)	544
21.4.10	St. John’s Wort (<i>Hypericum perforatum</i>)	545

21.4.11	Valerian (<i>Valeriana officinalis</i>)	546
21.5	Future Perspectives: Need for Evidence and Advice to Cancer Patients and Physicians	546
21.6	Conclusions	547
	Acknowledgments	547
	Conflict of Interest	547
	References	547
22	Quality Use of Medicines: Considerations in Phytotherapy	554
	<i>Lynn Weekes</i>	
22.1	Introduction	554
22.1.1	Judicious Use	554
22.1.2	Appropriate Selection	555
22.1.3	Safe and Effective Use	555
22.1.4	The QUM Paradigm	555
22.2	Relevance of QUM for Herbal Medicines	556
22.2.1	Is the QUM Framework Relevant for Herbal Therapies?	556
22.3	Use of Phytotherapies by Consumers	558
22.4	Consumer Attitudes and Beliefs about Herbal Medicines	559
22.4.1	Holistic View of Health and Well-Being	559
22.4.2	It is Natural, So it Must be Safe	560
22.5	Applying the QUM Framework to Phytotherapies	561
22.5.1	Judicious Use	561
22.5.2	Appropriate Selection	562
22.5.3	Safe and Effective Use	563
22.5.4	Adverse Reactions	563
22.5.5	Interactions	564
22.5.6	Allergy	565
22.5.7	Safe Formulation	565
22.5.8	Effectiveness	565
22.6	Building Blocks for Quality Use of Herbal Medicines	566
22.6.1	Objective Information and Ethical Promotion	566
22.6.2	Education and Training	568
22.6.3	Systems and Interventions	569
22.6.4	Shared Decision Making	569
22.7	Conclusion	570
	References	570
23	Intellectual Property and Patent Issues with Phytotherapy Products	573
	<i>Gint Silins, Jennifer Tan, and Kelvin Chan</i>	
23.1	Introduction	573
23.1.1	Historical and Current Aspects of Intellectual Property	573
23.1.2	Types of Intellectual Property Rights	574
23.1.3	Worldwide IP Laws Have Yet to Be Harmonized	575
23.2	IP Rights—Phyto-Industry	575

23.2.1	IP Protection for Phytotherapy Products and Phytotherapies	575
23.2.2	Patents	576
23.2.3	Patents as IP Assets	576
23.2.4	Patents for Protecting Phyto-Inventions	577
23.2.5	Exclusions to Patentability	577
23.3	Brief Overview of Patents and the Patenting Process	578
23.3.1	Patent Searching	578
23.3.2	Patent Ownership	578
23.3.3	Patent Filing	579
23.3.4	Examination and Classification	579
23.3.5	Allowance and Grant	579
23.3.6	Extension of Patent Term	579
23.4	Other Types of IP Rights	585
23.4.1	Trade Secrets	585
23.4.2	Regulatory Exclusivity and Restricted Third-Party Access	585
23.4.3	Plant Variety Protection	586
23.4.4	Industrial Designs	586
23.4.5	Trademarks	586
23.5	Patenting Trends for Phytotherapeutics	587
23.6	Traditional Knowledge and IP Rights	587
	Disclaimer	589
	References	590
24	International Regulatory Status of Phytotherapies	593
	<i>Ernest V. Linek</i>	
24.1	Introduction	593
24.1.1	Country Law Sources	594
24.1.2	Common Requirement: Good Manufacturing Practices	594
24.2	Specific Country Regulations	596
24.2.1	Current Regulations in Australia	596
24.2.2	Current Regulations in Canada	597
24.2.3	Current Regulations in China	604
24.2.4	Current Regulations in the European Union (EU)	609
24.2.5	Current Regulations in India	616
24.2.6	Current Regulations in Japan	619
24.2.7	Current Regulations: United Kingdom	622
24.2.8	Current Regulations in the United States	625
24.3	Future of Phytotherapies: World Health Organization (WHO)	631
	Further Reading	634
	Index	635

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
February 2015

1

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

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].