

CONTENTS

Contributors	xv
Preface	xix
1 Natural Products in Drug Discovery: Recent Advances	1
<i>Gordon M. Cragg, Paul G. Grothaus, and David J. Newman</i>	
1.1 Introduction	1
1.2 The Role of Traditional Medicine and Plants in Drug Discovery	2
1.3 The Role of Marine Organisms in Drug Discovery	4
1.4 The Role of Microorganisms in Drug Discovery: An Historical Perspective	6
1.5 Other Sources	8
1.6 The Importance of Natural Products in Drug Discovery and Development	8
1.7 Classical Natural Sources: Untapped Potential	10
1.8 The Unexplored Potential of Microbial Diversity	10
1.8.1 Improved Culturing Procedures	11
1.8.2 Extraction of Environmental Samples (the Metagenome)	11
1.8.3 Cryptic Clusters in Bacteria and Fungi	12
1.8.4 Marine Microbes	14
1.8.5 Cyanophytes	14
1.8.6 Microbial Symbionts	16
1.8.7 Plant Endophytes	16
1.8.8 Extremophiles	17
1.8.9 Combinatorial Biosynthesis	18

1.9	Development of Drugs From Natural Products: A Multidisciplinary Process	19
1.9.1	Synthesis Based on Natural Products	20
1.9.2	Natural Product-Inspired Combinatorial Synthesis	22
1.10	Conclusions	26
	References	27
2	Modern Approaches in the Search for New Active Compounds from Crude Extracts of Natural Sources	43
	<i>Emerson F. Queiroz, Kurt Hostettmann, and Jean-Luc Wolfender</i>	
2.1	Introduction	43
2.2	Selection of the Natural Matrices	45
2.3	Rapid Online Identification and Dereplication	46
2.4	HPLC-Hyphenated Methods for Natural Product Identification	46
2.4.1	HPLC Separation of Crude Extracts	46
2.4.2	LC-PDA	49
2.4.3	HPLC-MS	50
2.4.4	LC-NMR	53
2.4.5	SPE-NMR, Microflow NMR, and NMR with Cryogenized Probes	54
2.5	Studies on Natural Products Using LC-NMR, Microflow NMR, and SPE-NMR	57
2.5.1	Application of Online and At-Line LC-NMR Methods for Dereplication Studies	58
2.6	Application of Direct NMR Methods for Chemical Profiling of Crude Extracts	67
2.6.1	Application of Direct NMR Methods in Quality Control	67
2.6.2	Application of Direct NMR Methods in Metabolomics	68
2.7	Conclusions	69
	References	71
3	Natural Products as Lead Compounds in Medicinal Chemistry	81
	<i>Eliezer J. Barreiro, Carlos A. M. Fraga, and Lidia M. Lima</i>	
3.1	Medicinal Chemistry Definition and the Importance of the Lead Compound in Drug Discovery	81
3.2	Natural Products as Drugs	84
3.2.1	Digitalis	84
3.2.2	Alkaloids from Plants as Drugs	85
3.2.3	Penicillin and the Antibiotics Era	86
3.2.4	Anticancer Drugs	90
3.2.5	The Recent Discovery of Ziconotide as a Novel Analgesic Drug	96
3.3	Natural Products as Lead Compound for New Medicines Discovery	96
3.3.1	From Morphine (38) to Synthetic Hypnoanalgesic Drugs	96
3.3.2	Alkaloids as Source of Antimalarial Drugs	97

3.3.3	Ganglionic Blockers: The Drug Class of Amazon Natives	98
3.3.4	Antiviral Drugs from the Sea	100
3.3.5	From Prostaglandins Derived from Caribbean Corals to Misoprostol	100
3.3.6	Antiobesity Drugs Derived from Natural Products	101
3.3.7	The NP Inspiration to the Modern Synthetic Anticancer Class	102
3.3.8	Discovery of Statins: The Top-Class of Drug in the World Market from Fungi	103
3.4	Natural Products as Lead Compounds for New Drug Candidates	107
3.5	Conclusions	113
	Acknowledgments	115
	References	115
4	The Importance of Structural Manipulation of Natural Compounds in Drug Discovery and Development	127
	<i>Arturo San Feliciano, María Á. Castro, José L. López-Pérez, and Esther del Olmo</i>	
4.1	Introduction	127
4.2	Chemomodulation of Podophyllotoxin Cyclolignans	132
4.2.1	Chemomodulation of the Immunosuppressive Activity of Podolignans	135
4.2.2	Chemomodulation of Antineoplastic Potency and Selectivity of Podolignans	137
4.3	Chemoinduction of Bioactivity on Dihydrostilbenoids	140
4.3.1	Chemomodulation of the Vasorelaxant Activity of Phthalazinone IVa	143
4.3.2	Mechanistic and Structure–Activity Relationships Studies on the Vasorelaxant Activity of Phthalazinones	146
4.4	Chemoinduction and Chemomodulation of the Antiparasitic Activity of Stilbenoids	150
4.4.1	Antileishmanial Activity	150
4.4.2	Trypanocidal Activity	151
4.4.3	Antimalarial Activity	151
4.4.4	Studies on the Mechanism of Antiplasmodial Activity and <i>In Vivo</i> Assays	152
4.5	Conclusions	152
	Acknowledgments	153
	References	153
5	The Action of Plants and their Constituents on the Central Nervous System	161
	<i>Fúlvio R. Mendes, Giuseppina Negri, Joaquim M. Duarte-Almeida, Ricardo Tabach, and Elisaldo A. Carlini</i>	
5.1	Introduction	161

5.2	Plants with CNS Depressant Activity	162
5.2.1	Kava-kava: <i>Piper methysticum</i> Forst (Piperaceae)	163
5.2.2	Valerian: <i>Valeriana officinalis</i> L. (Valerianaceae)	164
5.2.3	Chamomile: <i>Matricaria chamomilla</i> L. (Asteraceae)	164
5.2.4	Balm, Lemon Balm: <i>Melissa officinalis</i> L. (Lamiaceae)	165
5.2.5	Hop: <i>Humulus lupulus</i> L. (Moraceae)	165
5.2.6	Tilia: <i>Tilia cordata</i> Mill. and <i>Tilia americana</i> var <i>mexicana</i> (Tiliaceae)	166
5.2.7	Bushy Lippia or Falsa Melissa: <i>Lippia alba</i> Mill (Verbenaceae)	166
5.2.8	Lemon Grass: <i>Cymbopogon citratus</i> (DC.) Stapf (Poaceae)	167
5.2.9	Erythrina: <i>Erythrina mulungu</i> Mart. ex Benth. and <i>Erythrina velutina</i> Wild (Leguminosae)	167
5.2.10	<i>Passiflora</i> genus (Passifloraceae)	168
5.2.11	Essential Oils	168
5.2.12	Other Plants with Depressant Action on the Central Nervous System	169
5.3	Plants with the CNS Stimulant Activity	169
5.3.1	Coffee: <i>Coffea arabica</i> L. (Rubiaceae)	170
5.3.2	Tea Plant: <i>Camellia sinensis</i> L. Kuntze (Theaceae)	171
5.3.3	Guarana: <i>Paullinia cupana</i> Kunth (Sapindaceae)	171
5.3.4	Mate: <i>Ilex paraguariensis</i> St. Hil. (Aquifoliaceae)	172
5.3.5	Ma Huang: <i>Ephedra sinica</i> Stapf (Ephedraceae)	172
5.3.6	Khat: <i>Catha edulis</i> Forsk (Celastraceae)	173
5.3.7	Cola nut: <i>Cola nitida</i> (Vent.) Schott et Endl. or <i>Cola acuminata</i> (Beauv.) Schott et Endl. (Sterculiaceae)	173
5.3.8	Coca: <i>Erythroxylum coca</i> Lam. (Erythroxylaceae)	174
5.4	Plants Used as Antidepressants	174
5.4.1	St. John's wort: <i>Hypericum perforatum</i> L. (Guttiferae)	174
5.4.2	Other Plants with Antidepressant Potential	175
5.5	Adaptogenic Plants	175
5.5.1	Ginseng: <i>Panax ginseng</i> C. A. Meyer (Araliaceae)	176
5.5.2	Siberian Ginseng: <i>Eleutherococcus senticosus</i> (Rupr. and Maxim.) Maxim. (Araliaceae)	177
5.5.3	Damiana: <i>Turnera diffusa</i> Willd. var. <i>aphrodisiaca</i> (Ward.) Urb. (Turneraceae)	177
5.5.4	Other Adaptogens	178
5.6	Plants Used to Treat Neurodegenerative Diseases	178
5.6.1	Ginkgo: <i>Ginkgo biloba</i> L. (Ginkgoaceae)	179
5.6.2	Dong Guai, Chinese Angelica: <i>Angelica sinensis</i> (Oliv.) Diels (Apiaceae)	179
5.6.3	Gotu kola: <i>Centella asiatica</i> (L.) Urban (Apiaceae)	180
5.6.4	Muirapuama: <i>Ptychopetalum olacoides</i> Benth. (Olacaceae)	180

5.6.5	The Cowhage, Velvet Bean: <i>Mucuna pruriens</i> (L.) DC. (Fabaceae)	180
5.6.6	Caffeine and Other Adenosinergic Antagonists as Neuroprotective Agents	181
5.6.7	Antioxidants and Anticholinesterasics of Natural Origin	181
5.7	Plants with the Mind-Altering Activity	182
5.7.1	Nutmeg: <i>Myristica fragrans</i> Houtt (Myristicaceae)	183
5.7.2	Mandrake: <i>Mandragora officinarum</i> L. (Solanaceae)	184
5.7.3	Marihuana, Hemp: <i>Cannabis sativa</i> L. (Cannabaceae)	185
5.7.4	Salvia: <i>Salvia divinorum</i> Eplin et Játiva-M. (Lamiaceae)	185
5.7.5	Peyote: <i>Lophophora williamsii</i> [Lem.] Coulter (Cactaceae)	186
5.7.6	Jurema: <i>Mimosa tenuiflora</i> [Willd.] Poir. (Fabaceae)	186
5.7.7	Ayahuasca	187
5.7.8	Other Mind-Altering Drugs	187
5.8	Plants Used Against Drug Dependence	188
5.9	Conclusions	188
	Acknowledgments	191
	References	191
6	The Role of Natural Products in Discovery of New Anti-Infective Agents with Emphasis on Antifungal Compounds	205
	<i>Maximiliano Sortino, Marcos Derita, Laura Svetaz, Marcela Raimondi, Melina Di Liberto, Elisa Petenatti, Mahabir Gupta, and Susana Zacchino</i>	
6.1	Infectious Diseases and Available Antimicrobial Agents	205
6.2	Fungal Infections and Available Antifungal Agents	206
6.2.1	Fungal Infections	206
6.2.2	Available Antifungal Drugs	206
6.3	The Need of New Antifungal Agents	208
6.3.1	Organisms Recently Investigated as Sources for Antifungal Compounds	208
6.3.2	Plants as Source of Antifungal Metabolites	208
6.3.3	Microorganisms as Source of Antifungal Metabolites	219
6.3.4	Marine Organisms as Sources of Antifungal Metabolites	220
6.4	From Antifungal Compounds to Antifungal Drugs: Some Considerations	223
6.5	Other Strategies Based on Non-targeted Assays	223
6.5.1	Screening of Extracts or Natural Products in Combination with Other Compounds	223
6.6	Strategies Based on Targeted Assays for the Discovery of Antifungal Compounds	226
6.6.1	Natural Products Inhibitors of Fungal Cell-Wall Assembly or Synthesis	226
6.6.2	Natural Products Inhibitors of the Fungal Cell Membrane	227

6.6.3	Natural Products Inhibitors of Virulence Factors	227
6.6.4	Discrimination of Modes of Action of Antifungal Substances by Use of Metabolic Foot Printing	227
6.6.5	New Targets Based on Genomics	228
6.7	Conclusion	229
	References	229
7	Antiulcer Agents from Higher Plants	241
	<i>Luiz C. Klein-Júnior, José R. Santin, and Sérgio F. de Andrade</i>	
7.1	Introduction	241
7.2	Medicinal Plants with Antiulcer Activity	243
7.2.1	Maytenus Genus	243
7.2.2	Glycyrrhiza Genus	248
7.2.3	Plants Investigated in our Laboratory	249
7.3	Secondary Metabolites as a Source of Anti-Ulcer Drug Leads	251
7.3.1	Effect on Endogenous Gastroprotective Factors	251
7.3.2	Protective Activity Against Aggressive Factors	254
7.4	Conclusions	256
	References	256
8	Recent Progress in the Chemistry and Biology of Paclitaxel (Taxol™) and Related Taxanes	263
	<i>Jun Qi, Jielu Zhao, and David G. I. Kingston</i>	
8.1	Introduction	263
8.2	New Chemistry of Paclitaxel	265
8.2.1	New Taxanes	265
8.2.2	New Chemistry of Paclitaxel	269
8.2.3	Paclitaxel Analogs	280
8.2.4	Biotechnological Production of Paclitaxel	294
8.3	Tubulin Binding	295
8.3.1	Binding Conformation of Paclitaxel to Tubulin	295
8.3.2	Synthetic Efforts to Make Conformationally Restricted Analogs of Paclitaxel	298
8.4	Pharmacology of Paclitaxel	306
8.4.1	Prodrugs and Drug Delivery of Paclitaxel	306
8.5	Conclusions	318
	References	319
9	Cancer Chemopreventive Activity of Higher Plants	337
	<i>A. Douglas Kinghorn, Yulin Ren, Jie Li, and Chung Ki Sung</i>	
9.1	Introduction	337
9.2	Potential Cancer Chemopreventive Agents from Selected Dietary Higher Plants	338

9.3	Conclusions	348
	Acknowledgments	348
	References	348
10	Medicinal Plants and Pharmaceutical Technology	359
	<i>Ruth M. Lucinda da Silva, Angélica G. Couto, and Tania M.B. Bresolin</i>	
10.1	Introduction	359
10.2	Supply of Herbal Materials	361
10.2.1	Cultivation of Medicinal Plants	361
10.3	Harvest and Postharvest Processing	363
10.3.1	Harvest	363
10.3.2	Postharvest Treatment	363
10.3.3	Pulverization	365
10.4	Extraction of Herbal Drugs	365
10.4.1	Extraction	365
10.4.2	Extraction Methods	366
10.4.3	Filtration	369
10.4.4	Clarification	369
10.4.5	Concentration: Partial Removal of the Solvent	369
10.4.6	Decontamination by Ionizing Radiation	369
10.5	Dry Extracts	369
10.6	Phytopharmaceutical Dosage Forms	373
10.6.1	Semisolid Dosage Forms	373
10.6.2	Solid Dosage Forms	375
10.7	Quality Assurance and Quality Control of Herbal Drugs and Phytopharmaceuticals	377
10.7.1	Recommended Procedures of Sampling of Material in Bulk	378
10.7.2	Parameters for Quality Control of Herbal Drugs	378
10.7.3	Parameters for Quality Control of Herbal Preparations	384
10.7.4	Parameters for Quality Control of Herbal Medicinal Product	385
	References	387
11	Natural Products in Clinical Trials	395
	<i>Sigrun Chrubasik</i>	
11.1	The Quality of Clinical Trials	395
11.2	Examples of Clinical Studies with Natural Products	396
11.2.1	An Observational Study with Potato Juice	396
11.2.2	A Randomized Double-Blind Study and a Cohort Study Investigating Two Doses of a Proprietary Willow Bark Extract in Low Back Pain Exacerbations	403
11.3	Evidence of Effectiveness	413
	References	416

12	The Influence of Biotic and Abiotic Factors on the Production of Secondary Metabolites in Medicinal Plants	419
	<i>Dayana R. Gouvea, Leonardo Gobbo-Neto, and Norberto P. Lopes</i>	
12.1	Introduction	419
12.2	Biotic and Abiotic Factors that can Affect Biosynthesis and/or Metabolites Accumulation	422
12.2.1	The Atmosphere's Chemical Composition	422
12.2.2	Pathogen Attacks, Mechanic Stimulus, and Herbivory	423
12.2.3	Temperature	425
12.2.4	Ultraviolet Radiation	426
12.2.5	Hydric Stress	428
12.2.6	The Soil Influence and Its Nutrients	430
12.3	Types of Observed Variations on Secondary Metabolites Content	431
12.3.1	Eco-Physiologic Variations on Secondary Metabolites Content	431
12.3.2	Secondary Metabolites Variation According to the Altitude	432
12.3.3	Rhythmical Variations and Ontogenesis	434
12.4	Conclusions	439
	References	440
13	Production of Bioactives Compounds: The Importance of Pictet–Spengler Reaction in the XXI Century	453
	<i>Pilar Menendez, Ilaria D'Acquarica, Giuliano Delle Monache, Francesca Ghirga, Andrea Calcaterra, Marco Barba, Alberto Macone, Alberto Boffi, Alessandra Bonamore, and Bruno Botta</i>	
13.1	Introduction	453
13.2	Variants and Applications	455
13.3	Asymmetric Synthesis	457
13.4	Chiral Auxiliary and Enantioselective Catalysis	459
13.5	Enzymatic Catalysis	465
13.6	The Pictet–Spengler Reaction at Present	468
13.6.1	Tetrahydroisoquinoline (THIQ) Family	468
13.6.2	Tetrahydro- β -Carbolines and Indole-Related Alkaloids	472
13.6.3	Novel Scaffolds and New Generation Substrates	475
13.7	Conclusions	478
	Acknowledgment	480
	References	480
14	Screening Methods for Drug Discovery from Plants	489
	<i>Alan L. Harvey</i>	
14.1	From Traditional to Phenotypic Screening	489
14.2	Molecular and Cellular Assays	490

14.3	Disease-Specific Assays	
14.3.1	Anticancer Drug Discovery	492
14.3.2	Diabetes and Metabolic Diseases	492
14.3.3	Antimicrobial Drug Discovery	493
14.3.4	Anti-Inflammatory Drug Discovery	493
14.4	Conclusions	494
	References	495
		495
15	Phytotherapeutics – Intellectual Property Rights, Global Market, and Global Regulatory Guidelines	499
	<i>James D. McChesney, Raymond Cooper, and Kip Vought</i>	
15.1	Intellectual Property Rights	499
15.2	Biodiversity	501
15.3	Global Market Perspectives	502
15.3.1	Veregen®/Polyphenon® E Ointment	504
15.3.2	Omacor	506
15.3.3	Generic Competition	507
15.4	Regulatory Perspectives	507
15.5	Conclusions	525
	References	526
16	Cooperation Between the Pharmaceutical Industry and Academic Institutions in Drug Discovery	529
	<i>Valdir Cechinel-Filho, Rivaldo Niero, and Rosendo A. Yunes</i>	
16.1	Introduction	529
16.2	Interaction Between Academic Institutions and the Pharmaceutical Industry	530
16.3	Overview of the Global Pharmaceutical Market	534
16.4	Reorganization of the Pharmaceutical Industry	535
16.4.1	Pharmaceutical Market in Brazil	536
16.4.2	The Behavior of Generic and Phytomedicines in Brazil	537
16.4.3	Acheflan: An Example of Brazilian Phytomedicine	539
16.5	Conclusions	541
	Acknowledgments	542
	References	542
	Index	545