

THERAPEUTIC USE OF PLANT SECONDARY METABOLITES



Editor:
Saheed Sabiu

Bentham Books

Therapeutic Use of Plant Secondary Metabolites

Edited by

Saheed Sabiu

*Department of Biotechnology and Food Science
Faculty of Applied Sciences
Durban University of Technology
Durban 4000
South Africa*

Vj gtr gwle'Wug'qhRrpvUgeqpf ct { 'O gwdqksgu

Editor: Saheed Sabiu

ISBN (Online): 978-981-5050-62-2

ISBN (Print): 978-981-5050-63-9

ISBN (Paperback): 978-981-5050-64-6

© 2022, Bentham Books imprint.

Published by Bentham Science Publishers Pte. Ltd. Singapore. All Rights Reserved.

First published in 2022.

BENTHAM SCIENCE PUBLISHERS LTD.

End User License Agreement (for non-institutional, personal use)

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the book/echapter/ejournal (“**Work**”). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: permission@benthamscience.net.

Usage Rules:

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

Disclaimer:

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

Limitation of Liability:

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

General:

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of Singapore. Each party agrees that the courts of the state of Singapore shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.

80 Robinson Road #02-00

Singapore 068898

Singapore

Email: subscriptions@benthamscience.net



CONTENTS

FOREWORD	i
PREFACE	ii
LIST OF CONTRIBUTORS	iii
CHAPTER 1 THE ROLE OF PLANT SECONDARY METABOLITES IN HEALTH MANAGEMENT	1
<i>Taofik Olatunde Uthman</i>	
1. INTRODUCTION	1
2. CLASSIFICATION OF PLANT SECONDARY METABOLITES	3
3. POLYPHENOLS – A MAJOR CLASS OF PLANT SECONDARY METABOLITES	3
3.1. Classes of Polyphenols	3
3.1.1. Phenolic Acids	4
3.1.2. Flavonoids	5
3.1.3. Lignans and Stilbenes	6
4. MEDICINAL PLANTS	6
5. PLANTS SECONDARY METABOLITES IN HEALTH MANAGEMENT	7
5.1. Alkaloids	7
5.2. Flavonoids	8
5.3. Terpenes	9
5.4. Saponins	11
CONCLUSION	12
CONSENT FOR PUBLICATION	12
CONFLICT OF INTEREST	12
ACKNOWLEDGEMENTS	13
REFERENCES	13
CHAPTER 2 MEDICINAL PLANTS AND DRUG DISCOVERY	21
<i>Emmanuel O. Ajani</i>	
1. INTRODUCTION	21
2. HISTORICAL USE OF PLANTS FOR PHARMACOLOGICAL PURPOSES	23
3. THE PROCESS AND TECHNIQUES OF DRUG DEVELOPMENT FROM PLANTS ...	26
Phase I: Collection and Identification	28
Phase II: Isolation and Purification	28
Phase III: Synthesis of the Bioactive Compound	29
Phase IV: Clinical Trials	30
4. PLANTS BIOACTIVE COMPOUNDS AND THEIR APPLICATIONS IN SOME DISEASES	30
4.1. Plants Bioactive Compounds as Anticancer Agents	30
4.2. Plants Bioactive Compounds as Antimalarial Agents	31
4.3. Plants Bioactive Compounds as Antiviral Agents	31
5. PLANT-BASED DRUG AND THE CHALLENGE OF EMERGING INFECTIOUS DISEASES: COVID-19 EXPERIENCE	32
6. APPLICATION OF EMERGING TECHNOLOGIES IN PROMOTING DRUG DISCOVERY FROM PLANTS	33
(a). Proteomics, Genomics and Bioinformatics	34
(b). Combinatorial Chemistry	35
(c). High-Throughput Screening (HTS)	36
7. CHALLENGES TO DRUG DISCOVERY FROM PLANTS	37
8. DRUG DISCOVERY FROM PLANTS: THE CHALLENGE FOR AFRICA	39

9. FUTURE PROSPECT OF PLANT-BASED DRUGS	40
CONCLUDING REMARKS AND FUTURE PERSPECTIVE	40
CONSENT FOR PUBLICATION	41
CONFLICT OF INTEREST	41
ACKNOWLEDGEMENTS	41
REFERENCES	41
CHAPTER 3 THERAPEUTIC PROPERTIES OF BIOACTIVE SECONDARY METABOLITES IN ESSENTIAL OIL CROPS	50
<i>Fikisiwe C. Gebashe, Adeyemi O. Aremu and Stephen O. Amoo</i>	
1. INTRODUCTION	51
2. SECONDARY METABOLITES AND THEIR ROLE IN PLANTS	52
3. MAJOR BIOACTIVE SECONDARY METABOLITES FROM ESSENTIAL OILS OF SELECTED MEDICINAL HERBS	53
4. PHARMACOLOGICAL PROPERTIES OF ESSENTIAL OILS MAJOR COMPOUNDS	55
4.1. Antimicrobial Activity	55
4.2. Anti-inflammatory	69
4.3. Antioxidants	71
4.4. Cytotoxicity	73
CONCLUDING REMARKS	75
CONSENT FOR PUBLICATION	75
CONFLICT OF INTEREST	75
ACKNOWLEDGEMENTS	75
REFERENCES	76
CHAPTER 4 BIOACTIVE COMPOUNDS AS THERAPEUTIC INTERVENTION IN CANCER THERAPY	84
<i>Depika Dwarka, Himansu Baijnath and John Jason Mellem</i>	
1. INTRODUCTION	84
2. CANCER AND APOPTOSIS	85
2.1. Global Prevalence of Cancer	85
2.2. General Features of Cancer	86
2.3. Pathophysiology of the Carcinogenic Process	86
2.4. Apoptosis: Hallmark of Cancer Development and Progression	88
2.5. Free Radicals and Anti-oxidants in Relation to Cancer Inflammation	89
3. MEDICINAL PLANTS: THEIR USE IN ANTI-CANCER TREATMENT	90
3.1. Plant Based Chemotherapeutics	91
3.1.1. <i>Camptothecin</i>	91
3.1.2. <i>Paclitaxel and Docetaxel</i>	92
3.1.3. <i>Colchicine</i>	93
3.1.4. <i>Vinca Alkaloids</i>	94
3.1.5. <i>Homoharringtonine</i>	95
3.1.6. <i>Podophyllotoxin</i>	96
3.2. Other Plant-based Compounds of Importance in Cancer Treatment	97
3.2.1. <i>Phenolic Compounds</i>	97
3.2.2. <i>Alkaloids</i>	100
3.2.3. <i>Polysaccharides</i>	100
3.2.4. <i>Terpenoids</i>	101
3.2.5. <i>Quinones</i>	103
CONCLUSION	104
CONSENT FOR PUBLICATION	104
CONFLICT OF INTEREST	104

ACKNOWLEDGEMENTS	104
REFERENCES	104
CHAPTER 5 BIOACTIVE COMPOUNDS AS THERAPEUTIC INTERVENTION IN MUCOCUTANEOUS CANCERS	111
<i>Henry A. Adeola, Rashmi Bhardwaj, Aderonke F. Ajayi-Smith, Afsareen Bano, Tayo A. Adekiya, Michael C. Ojo, Raphael T. Aruleba, Adeniyi C. Adeola, Babatunji E. Oyinloye and Chinedu E. Udekwu</i>	
1. INTRODUCTION TO MUCOSAL AND SKIN CANCERS	112
1.1. Melanomas	113
1.2. Basal Cell Carcinoma	113
1.3. Squamous Cell Carcinoma	114
2. CONVENTIONAL MUCOCUTANEOUS CANCER THERAPY	114
2.1. Surgical Excision of Mucocutaneous Cancers	115
2.2. Non-surgical Treatment of Mucocutaneous Cancers	115
3. TARGETED MUCOCUTANEOUS CANCER THERAPIES	117
3.1. Purine/Pyrimidine Analogues	117
3.2. Photodynamic Therapy (using Antioxidants)	117
3.3. Bioactive Compound and Photodynamic Therapy-carotenoids, Flavonoids and Terpenoids	118
3.4. Emerging Targeted Molecular Therapies-Obstacles and Opportunities	118
4. BIOACTIVE COMPOUNDS AS POTENTIAL TARGETS FOR MUCOCUTANEOUS CANCERS	119
5. BIOACTIVE COMPOUNDS AND OMICS APPROACH IN MUCOCUTANEOUS CANCERS	121
6. BIOACTIVE COMPOUNDS AND IMPORTANCE IN THE TREATMENT OF MUCOCUTANEOUS CANCERS	122
6.1. Bioactive Compounds with Anti-skin Cancer Property	122
6.1.1. Curcumin	122
6.1.2. Myricetin	123
6.1.3. Tocotrienol	123
7. NOVEL APPLICATIONS OF BIOACTIVE FLAVONOID COMPOUNDS FOR MUCOCUTANEOUS CANCER MANAGEMENT	123
CONCLUSION AND FUTURE PERSPECTIVES	127
CONSENT FOR PUBLICATION	127
CONFLICT OF INTEREST	127
ACKNOWLEDGEMENTS	127
AUTHORS' CONTRIBUTIONS	127
REFERENCES	128
CHAPTER 6 BIOACTIVE COMPOUNDS AS THERAPEUTIC INTERVENTION IN BACTERIAL INFECTIONS	139
<i>Kazeem A. Alayande, Abdulwakeel A. Ajao and Mariam O. Oyedeji-Amusa</i>	
1. INTRODUCTION	140
2. DIFFICULTIES IN THE TREATMENT OF BACTERIAL INFECTIONS	143
3. WHAT BIOACTIVE COMPOUNDS DO DIFFERENTLY	145
3.1. Efficiency of Bioactive Compounds against Bacterial Pathogens	147
3.2. Phenols and Phenolic Compounds	148
3.3. Alkaloids	149
3.4. Tannins	149
3.5. Terpenoids and Terpenes	150
3.6. Saponins	151

3.7. Flavonoids	151
3.8. Bioactive Peptides	152
CONCLUSION	153
CONSENT FOR PUBLICATION	153
CONFLICT OF INTEREST	153
ACKNOWLEDGEMENTS	153
REFERENCES	153
CHAPTER 7 THE USE OF PLANT SECONDARY METABOLITES IN THE TREATMENT OF BACTERIAL DISEASES	161
<i>Pillay Charlene, Ramdhani Nishani and Singh Seema</i>	
1. INTRODUCTION	161
2. GROUPS OF SECONDARY METABOLITES WITH ANTIBACTERIAL ACTIVITIES	165
Terpenes	165
Phenolics	166
<i>Flavonoids</i>	166
<i>Tannins</i>	168
<i>Coumarins</i>	168
<i>Quinones</i>	169
Nitrogen Containing Compounds	169
<i>Alkaloids</i>	169
Sulphur Containing Compounds	170
<i>Allicin</i>	170
<i>Ajoene</i>	171
<i>Sulforaphane</i>	171
3. THE MODE OF ACTION OF SECONDARY METABOLITES ON MICROBIAL CELLS	171
CONCLUSION	175
CONSENT FOR PUBLICATION	175
CONFLICT OF INTEREST	175
ACKNOWLEDGEMENTS	175
REFERENCES	175
CHAPTER 8 PLANT SECONDARY METABOLITES IN THE MANAGEMENT OF DEGENERATIVE DISEASES	185
<i>Judith N. Ohanaka, Uwazie C. Kenneth, Fatai O. Balogun and Saheed Sabiu</i>	
1. INTRODUCTION	186
2. SECONDARY METABOLITES	187
2.1. Major Classifications of Secondary Metabolites	187
2.1.1. <i>Terpenoids</i>	187
2.1.2. <i>Phenolics</i>	189
2.1.3. <i>Alkaloids</i>	190
3. SECONDARY METABOLITES IN THE MANAGEMENT OF BACTERIAL INFECTIONS	191
4. SECONDARY METABOLITES IN THE MANAGEMENT OF VIRAL INFECTIONS	194
5. SECONDARY METABOLITES IN THE MANAGEMENT OF MALARIA DISEASES	197
6. SECONDARY METABOLITES IN CANCER MANAGEMENT	200
7. SECONDARY METABOLITES IN DIABETES MELLITUS MANAGEMENT	203
CONCLUDING REMARKS	206
CONSENT FOR PUBLICATION	206
CONFLICT OF INTEREST	206
ACKNOWLEDGEMENTS	206

REFERENCES	206
CHAPTER 9 BIOACTIVE COMPOUNDS AS THERAPEUTIC INTERVENTION IN NEURODEGENERATIVE DISEASES	214
<i>N. Suleiman, I. Bulama and L.S. Bilbis</i>	
1. INTRODUCTION	214
2. BIOACTIVE CHEMICALS	215
2.1. Role and Types of Bioactive Compounds	216
2.1.1. Phenolic Compounds	216
2.1.2. Omega-3 Fatty Acids and Fat-Soluble Vitamins	218
2.1.3. Isothiocyanates	219
2.1.4. Carotenoids	220
2.1.5. Mind Food	221
2.2. Application of Some of the Bioactive Compounds in the Treatment of Neurodegenerative Diseases	221
2.3. Constituents of Bioactive compounds	223
2.3.1. Flavonoids	223
2.3.2. Anthocyanins	224
2.3.3. Tannins	225
2.3.4. Betalins	225
2.3.5. Carotenoids	226
2.3.6. Plant Sterols	227
2.3.7. Glucosinolates	228
3. NEURODEGENERATIVE DISEASES	228
3.1. Most Common Neurodegenerative Diseases	229
3.1.1. Alzheimer's disease (AD)	229
3.1.2. Parkinson disease (PD)	230
3.1.3. Huntington's Disease (HD)	231
3.1.4. Stroke	232
3.2. Pathophysiology of Neurodegenerative Diseases	233
CONCLUSION	235
CONSENT FOR PUBLICATION	235
CONFLICT OF INTEREST	235
ACKNOWLEDGEMENTS	235
REFERENCES	235
CHAPTER 10 GREEN SYNTHESIS APPLICATION IN DIABETES THERAPY	238
<i>Fatai O. Balogun and Saheed Sabiu</i>	
INTRODUCTION	238
Nano-synthesis Methods	240
Characterization of Nanoparticles	240
Green Synthesis of Nanoparticles	240
Interplay between Diabetes Mellitus, Medicinal Plants, and Nanotechnology	241
Safety Concerns	250
Mechanism of Action (MOA)	257
MATERIALS AND METHODOLOGY	257
DISCUSSION	258
CONCLUSION	260
CONSENT FOR PUBLICATION	260
CONFLICT OF INTEREST	260
ACKNOWLEDGEMENTS	261
REFERENCES	261

CHAPTER 11 AN UPDATE ON GREEN SYNTHESIS APPLICATION IN CANCER THERAPY	269
<i>Karishma Singh and Saheed Sabiu</i>	
1. INTRODUCTION	269
2. GREEN SYNTHESIZED NANOPARTICLES IN CANCER THERAPY	270
2.1. Silver	271
2.2. Gold	271
2.3. Zinc Oxide	272
2.4. Mechanism of Action of AgNPs, AuNPs, and ZnONPs Against Cancer Cells	273
3. GREEN SYNTHESIS AND CHARACTERIZATION OF NANOPARTICLES	274
3.1. The Biological Approaches	274
3.2. Synthesis Using Microorganisms	275
3.2.1. <i>Bacteria</i>	275
3.2.2. <i>Fungi</i>	276
3.2.3. <i>Cyanobacteria</i>	277
3.2.4. <i>Algae</i>	277
3.3. Plant Extracts	277
3.4. Enzymes and Biomolecules	278
3.5. Characterization of Nanoparticles	279
4. Application of Green Synthesized Nanoparticles in Cancer Therapy	282
5. The Pros and Cons of Green Synthesized Nanoparticles in Cancer Therapy	289
CONCLUDING REMARKS AND PERSPECTIVES	291
CONSENT FOR PUBLICATION	292
CONFLICT OF INTEREST	292
ACKNOWLEDGEMENTS	292
REFERENCES	292
CHAPTER 12 OXIDATIVE STRESS INVOLVEMENT IN ANTIBACTERIAL THERAPY	297
<i>Christiana E. Aruwa and Saheed Sabiu</i>	
1. INTRODUCTION	297
2. DISCUSSION	299
2.1. Sources of Oxidative Stress	299
2.2. Mechanism of Action of Antibacterial Agents	299
2.3. The Antimicrobial Lethality-Oxidative Stress Link	301
2.3.1. <i>Additional Notes and Considerations</i>	305
2.3.2. <i>Factors Impacting OS-mediated Antibacterial Therapy and Efficacy</i>	307
2.4. Adaptations in OS and Antimicrobial Therapy	308
2.5. Oxidative Stress Assessment	311
CONCLUDING REMARKS AND PERSPECTIVES	312
CONSENT FOR PUBLICATION	313
CONFLICT OF INTEREST	313
ACKNOWLEDGEMENTS	313
REFERENCES	313
CHAPTER 13 PHYTOTHERAPY AND THE ‘OMICS CONCEPT	323
<i>Ismaila O. Nurain</i>	
1. INTRODUCTION	323
2. THE ‘OMICS CONCEPT IN PHYTOTHERAPY	327
2.1. ‘OMICS Concept in Phytotherapy at DNA Level	327
2.2. ‘OMICS Concept in Phytotherapy at the RNA Level	329
2.3. ‘OMICS Concept in Phytotherapy at Protein Level	330

2.4. 'OMICS Concept in Phytotherapy at Metabolites Level	332
2.5. 'OMICS Concept in Phytotherapy at the Electrolytes Level	334
2.6. 'OMICS Concept in the Phytotherapy at the Cellular Level	334
CONCLUSION	335
CONSENT FOR PUBLICATION	335
CONFLICT OF INTEREST	335
ACKNOWLEDGEMENTS	335
REFERENCES	335
CHAPTER 14 PHYTOINFORMATICS IN DISEASE MANAGEMENT	343
<i>Ismaila O. Nurain</i>	
1. INTRODUCTION	343
2. RELEVANCE OF MEDICINAL PLANTS IN DISEASE MANAGEMENT	345
3. MEDICINAL PLANT INFORMATICS AND APPLICATION IN DISEASE MANAGEMENT	346
COMPUTATIONAL GENOMICS ANALYSIS	348
COMPUTATIONAL TRANSCRIPTOMICS ANALYSIS	353
COMPUTATIONAL PROTEOMICS ANALYSIS	354
COMPUTATIONAL METABOLOMICS ANALYSIS	354
4. NON-EXHAUSTIVE LIST OF DATABASES AND TOOLS FOR PHYTOINFORMATICS	356
5. FROM DATA ACQUISITION TO DISEASE MANAGEMENT	356
CONCLUSION	357
CONSENT FOR PUBLICATION	358
CONFLICT OF INTEREST	358
ACKNOWLEDGEMENTS	358
REFERENCES	358
CHAPTER 15 COMPUTATIONAL APPLICATIONS IN THE DRUG DISCOVERY AND DEVELOPMENT PROCESSES	365
<i>M.O. Kaka, J.O. Aribisala, S. Karishma, A.K. Oyebamiji, T.A. Ajayeoba, N.J. Ohanaka and S. Sabiu</i>	
1. INTRODUCTION	366
2. HISTORY OF DRUGS DISCOVERY, DESIGN AND DEVELOPMENT	368
3. CHALLENGES INVOLVED WITH CONVENTIONAL METHODS OF DRUG DEVELOPMENT	369
4. ADVANCES IN DRUGS DISCOVERY AND DEVELOPMENT PROCESSES	372
4.1. Advances in Microscopy	372
4.2. The Rise of Gene-editing Technologies	374
4.3. Other Advances	375
5. ROLE AND SIGNIFICANCE OF COMPUTATIONAL APPLICATIONS IN TRANSLATIONAL SCIENCE/PERSONALIZED MEDICINE	375
5.1. Computer-aided Drug Discovery	376
5.2. Therapeutic Targets in Degenerative and Microbial Diseases	378
5.3. Application of Molecular Dynamics Simulation in the Drug Discovery and Development Processes for Degenerative and Microbial Diseases	380
5.4. Diabetes	381
5.5. Cancer	382
5.6. Malaria	384
5.7. Bacterial, Fungal and Viral Infections	386
6. CHALLENGES WITH COMPUTATIONAL APPLICATIONS IN THE DRUG DISCOVERY PROCESS	387

7. RECENT AND EMERGING ROLES OF COMPUTATION APPLICATIONS IN DRUG	
DISCOVERY	388
Progress in Molecular Targeted Therapies	388
CONCLUSION AND PERSPECTIVES	389
CONSENT FOR PUBLICATION	390
CONFLICT OF INTEREST	390
ACKNOWLEDGEMENTS	390
REFERENCES	390
SUBJECT INDEX	624

FOREWORD

For centuries, plants have played vital roles in biological beings' economic, social, spiritual, cultural and health wellbeing. Interestingly, through knowledge and advances in research and technology, human beings are gaining a deeper understanding of the significant contributions of plants to human and animal health and development. There is abundant evidence showing that medicinal plants and their secondary metabolites are useful in preventing, ameliorating and in the treatment of various disease conditions such as diabetes, cancer, bacterial, fungal and viral infections. I am aware that many books on medicinal plants and secondary metabolites are in the market and university libraries. However, the current book on “Therapeutic use of plant secondary metabolites” is unique in its content, diversity, and originality of materials. Its depth and expertise of various national and international contributors make it a must-have and a must-read for scientists in the field of medicinal plants, agriculture, food science, postgraduate students, health professionals, and traditional healers. The book covers important topics such as drug discovery and their metabolites in health management, plant secondary metabolites as therapeutic agents in degenerative and microbial infections, etc. The topics are well-structured, covering 15 chapters (chapters 1-15). These topics/chapters provide a framework and stimuli for further in-depth research in the field.

I strongly endorse the book.

Oluwafemi Omoniyi Oguntibeju
Department of Biomedical Sciences
Faculty of Health & Wellness Sciences
Cape Peninsula University of Technology
Bellville, South Africa

PREFACE

The concept of phytotherapy is as old as mankind. During the last decades, it has become evident that there exist several plants with therapeutic potential, and it is increasingly being accepted that phytotherapy could offer potential lead compounds in the drug discovery/development process. The interest in phytotherapy could be associated with secondary metabolites that could act individually, additively, or in synergy to improve health and wellbeing. Indeed, medicinal plants, unlike conventional drugs, commonly have bioactive constituents working together catalytically and synergistically to produce a combined effect that may surpass the total activity of the individual constituents. The combined actions of these metabolites tend to increase the activity of the main constituent by speeding up or slowing down its metabolism in the body. Also, the secondary metabolites might minimize the rate of undesired adverse effects, and have an additive, potentiating, or antagonistic effect.

The book offers evidence-based mechanistic views on complementary and alternative medicine with a focus on biological mechanisms of action of plant secondary metabolites in degenerative and microbial diseases such as diabetes, cancer, neurodegenerative disorders, antimicrobial resistance, etc., while reporting health benefits. The chapters are written by enviable scholars, lecturers, and experts in indigenous knowledge systems (IKS), industrial and medicinal plants, phytotherapeutics, and phytoinformatics. **Therapeutic Uses of Plant Secondary Metabolites** is timely and highly valuable for both undergraduate and postgraduate students, as well as researchers and professionals in IKS, phytomedicine, ethnopharmacology, phytopharmacology, plant biotechnology, drug discovery and development, and phytotherapeutics.

Saheed Sabiu

Department of Biotechnology and Food Science
Faculty of Applied Sciences
Durban University of Technology
Durban 4000
South Africa

List of Contributors

- A.K. Oyebamiji** Computational Chemistry Research Laboratory, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria
- Adeyemi O. Aremu** Indigenous Knowledge Systems (IKS) Centre, North-West University, Faculty of Natural and Agricultural Sciences, Private Bag X2046, Mmabatho 2790, South Africa
School of Life Sciences, Scottsville 3209, University of KwaZulu-Natal Pietermaritzburg, Private Bag X01, Scottsville 3209, South Africa
- Aderonke F. Ajayi-Smith** International Centre for Genetic Engineering and Biotechnology (ICGEB), Cape Town, South Africa
- Adeniyi C. Adeola** State Key Laboratory of Genetic Resources and Evolution, Yunnan Laboratory of Molecular Biology of Domestic Animals, Kunming Institute of Zoology, Chinese Academy of Sciences, China
- Abdulwakeel A. Ajao** Department of Botany and Plant Biotechnology, University of Johannesburg, PO Box 524, Auckland Park 2006, Johannesburg, South Africa
- Babatunji E. Oyinloye** Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Science, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, York Road, Parktown, South Africa
Phytomedicine, Biochemical Toxicology and Biotechnology Research Laboratories, Department of Biochemistry, Faculty of Sciences, Afe Babalola University, Ado Ekiti, Nigeria
- Bulama I.** Department of Veterinary Physiology and Biochemistry, University of Maiduguri, Maiduguri, Nigeria
- Bilbis L.S.** Department of Biochemistry, Usmanu Danfodiyo University Sokoto, Nigeria
- Chinedu E. Udekwu** Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria
- Christiana E. Aruwa** Department of Biotechnology and Food Science, Durban University of Technology, P.O.Box 1334, Durban 4000, South Africa
- Depika Dwarka** Durban University of Science, Department of Biotechnology and Food Science, Durban, KwaZulu-Natal, South Africa
- Emmanuel O. Ajani** Department of Medical Biochemistry and Pharmacology, Kwara State University, Malete, P.M.B. 1530, Ilorin, Nigeria
- Fatai O. Balogun** Department of Biotechnology and Food Science, Durban University of Technology, P.O.Box 1334, Durban 4000, South Africa
- Fikisiwe C. Gebashe** Agricultural Research Council – Vegetables, Industrial and Medicinal Plants, Pretoria, Private Bag X293, Pretoria 0001, South Africa

- Henry A. Adeola** Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and Tygerberg Hospital, Cape Town, South Africa
Division of Dermatology, Department of Medicine, Faculty of Health Sciences and Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
- Himansu Baijnath** University of KwaZulu-Natal, School of Biological Sciences, Durban, South Africa
- Ismaila O. Nurain** Department of Pharmacology, The University of Minnesota Medical School, Minneapolis, USA
- J.O. Aribisala** Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, South Africa
- John Jason Mellem** Durban University of Technology, Department of Biotechnology and Food Science, Durban, KwaZulu-Natal, South Africa
- Karishma Singh** Department of Biotechnology and Food Science, Durban University of Technology, P.O.Box 1334, Durban 4000, South Africa
- Kazeem A. Alayande** Antibiotic Resistance and Phage Biocontrol Research Group, Department of Microbiology, North-West University, Mmabatho 2745, South Africa
Unit for Environmental Sciences and Managements, North-West University, Potchefstroom, South Africa
- M.O. Kaka** Department of Microbiology, Adeleke University, Ede, Osun State, Nigeria
- Michael C. Ojo** Department of Biochemistry and Microbiology, University of Zululand, KwaDlangezwa, South Africa
- Mariam O. Oyedeji-Amusa** Department of Botany and Plant Biotechnology, University of Johannesburg, PO Box 524, Auckland Park 2006, Johannesburg, South Africa
- Ohanaka N.J.** Department of Biochemistry, Nile University of Nigeria, Abuja, Nigeria
- Pillay Charlene** Department of Biotechnology and Food Science, Durban University of Science, Durban, South Africa
- Ramdhani Nishani** Council for Scientific and Industrial Research, Durban, South Africa
- Raphael T. Aruleba** Department of Molecular and Cell Biology, Faculty of Science, University of Cape Town, Cape Town, South Africa
- Rashmi Bhardwaj** Centre for Medical Biotechnology, Maharshi Dayanand University, Rohtak, Haryana, India
- Saheed Sabiu** Department of Biotechnology and Food Science, Durban University of Technology, P.O.Box 1334, Durban 4000, South Africa
- Singh Seema** Subinite (Pty) Ltd, Godrej Consumer Products South Africa, Durban, South Africa

- Stephen O. Amoo** Agricultural Research Council – Vegetables, Industrial and Medicinal Plants, Pretoria, Private Bag X293, Pretoria 0001, South Africa
Indigenous Knowledge Systems (IKS) Centre, North-West University, Faculty of Natural and Agricultural Sciences, Private Bag X2046, Mmabatho 2790, South Africa
Department of Botany and Plant Biotechnology, Faculty of Science, University of Johannesburg, P.O. Box 524, Auckland Park 2006, South Africa
- Suleiman N.** Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, Usmanu Danfodiyo University Sokoto, Sokoto, Nigeria
- T.A. Ajayeoba** Department of Microbiology, Adeleke University, Ede, Osun State, Nigeria
- Taofik Olatunde Uthman** School of Medicine and Department of Biological Sciences, University of Limerick, Limerick, Ireland
- Tayo A. Adekiya** Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Science, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, York Road, Parktown, South Africa
- Uwazie C. Kenneth** Department of Biochemistry, Nigeria, Ladoko Akintola University of Nigeria, Ogbomoso, Oyo State, Nigeria

CHAPTER 1

The Role of Plant Secondary Metabolites in Health Management

Taofik Olatunde Uthman^{1,*}

¹ *School of Medicine and Department of Biological Sciences, University of Limerick, Limerick, Ireland*

Abstract: Plant secondary metabolites (PSM) are bioactive compounds produced by plants for protection against predatory organisms and to attract insects for pollination. Recently, greater attention is being focused on PSM due to their perceived ability to elicit pharmacological activities, including antihypertensive, antiarrhythmic, antimalarial, anticancer, analgesic, antispasmodic, antidiabetic, and antimicrobial effects. Therefore, many plant species are continually screened for PSM, such as alkaloids, flavonoids, terpenes, saponins, cardiac glycosides, fatty acids, steroids, and tannins with a view to exploiting them in the manufacture of drugs and pharmaceuticals. In this review, the pharmacological activities and possible mechanisms of action of selected PSM are discussed.

Keywords: Alkaloids, Biological activity, Flavonoids, Polyphenols, Secondary metabolites, Saponins, Terpenes.

1. INTRODUCTION

The term ‘metabolites’ refers to intermediates and products of metabolism. They are usually small molecules with diverse functions, including structural, signaling, stimulatory, inhibitory, catalytic and defensive roles as well as providing fuel. Metabolites in plants can be of two types namely primary and secondary metabolites. Primary metabolites in plants are essential for life processes such as growth and development of cells. They are produced continuously during growth phase of plants where they are involved in important metabolic processes such as photosynthesis and respiration. Primary metabolites are generally heavy molecular weight compounds with diverse structures, including DNA, proteins, carbohydrates, and lipids.

* **Corresponding author Taofik Olatunde Uthman:** School of Medicine and Department of Biological Sciences, University of Limerick, Limerick, Ireland; E-mail: taofik.uthman@ul.ie

Unlike primary metabolites, secondary metabolites refer to a vast and diverse group of active organic compounds produced by plants for the purpose of increasing the likelihood of their survival by repelling or attracting other organisms. This implies that secondary metabolites play a defensive role against herbivory and other interspecies protection. They are not essential for the growth and development of the producing plants and are often differentially distributed among limited taxonomic groups within the plant kingdom. Their absence does not result in plant death but can impair survivability, fecundity, and aesthetics of plants. Apart from the protective role, some secondary metabolites are involved in the pigmentation of flower and seed, which attract pollinators, thereby enhancing seed dispersal and plant reproduction. More importantly, plant secondary metabolites have been reported to possess a myriad of pharmaceutical properties which can be exploited for human health [1]. Secondary metabolites are biosynthesized from primary metabolites by specialized cell types at distinct developmental stages. They are generally low molecular weight compounds, varying in quality and quantity for a specific plant species depending on location.

The main biotic factor that affects plants is a pathogenic infection caused by bacteria, viruses, fungi, and nematodes. Other biotic antagonists include attacks by mites, insects, mammals, and other herbivorous animals and competition from other plants arising from parasitism and allelopathy. The most significant abiotic environmental stresses faced by plants are excessive temperature and water as well as exposure to radiation and chemicals. To combat these stress factors, plants have evolved a defensive system involving the production of secondary metabolites, which serve to protect against predators and microbial pathogens [2]. These natural products are able to perform a defensive role due to their toxic nature, which allows them to repel herbivores and microbes as well as dominate other plants within the same locality [3]. One of the mechanisms employed by secondary metabolites is acting as antimicrobial agents, which may be pre-formed or induced by infection. Other modes of defense include formation of polymeric barriers to prevent penetration of pathogens, and synthesis of enzymes capable of degrading pathogenic cell wall. It is also possible for plants to employ secondary metabolites as specific recognition and signaling systems, which allows rapid detection of pathogenic invasion and triggering of defensive responses.

Plants can also efficiently respond to environmental stresses through sensors regulated by feedback mechanisms. To achieve this, plants use secondary metabolites as messengers under sub-optimal conditions to trigger their defense mechanism, which involves the production of phytochemicals, hormones and a variety of proteins necessary to protect the ultra-structure of plants from such hazards [4]. Elevated synthesis of secondary metabolites has also been observed under abiotic stresses like salinity and drought. These are utilized efficiently in

defense mechanisms and biochemical pathways facilitating water and nutrient acquisition, chloroplast function, ion uptake and balance, synthesis of osmotically active metabolites and specific proteins, production of metabolites acting as osmo-protectants and detoxifying radicals [5].

2. CLASSIFICATION OF PLANT SECONDARY METABOLITES

It has been estimated that well over 300,000 secondary metabolites exist in nature [6]. There is no rigid scheme for classifying these secondary metabolites due to their immense diversity with respect to structure, function, and biosynthesis. Hence, it is difficult for them to fit perfectly into a few simple categories. For ease of reference, PSM may be grouped based on the presence of a recurring structural feature. For example, flavonoid compounds are oxygenated derivatives of aromatic ring structure, while alkaloids having an indole ring are called indole alkaloids. Terpenes consist of five carbon isoprene units, which are assembled in different ways.

PSM may also be classified according to the genus to which the plant source belongs. For example, morphine and codeine are examples of opium alkaloids. Grouping is also possible according to biological activities and physiological effects they elicit, such as antimicrobials, antibiotics, analgesics, *etc.* PSM can also be classified based on similarities in biosynthetic pathways. Generally, classifications based on structure and biosynthesis are more realistic and make the most sense.

3. POLYPHENOLS – A MAJOR CLASS OF PLANT SECONDARY METABOLITES

Polyphenols are secondary metabolites essential for the protection and survival of plants. They represent one of the most widespread groups of secondary metabolites in plants, with more than 8,000 identified phenolic structures [7]. These compounds can be found in almost all organs of plants, where they perform a myriad of functions, including skeletal constituents of different tissues and pigmentation of several plant organs [8], defense against various pathogens [9] and signaling molecules in plant cells [10]. The main sources of phenolic compounds are woody vascular plants, especially bark.

3.1. Classes of Polyphenols

Fig. (1) depicts the sub-divisions of polyphenols into different classes based on their chemical structures, namely phenolic acids, flavonoids, stilbenes and lignans [11, 12].

Medicinal Plants and Drug Discovery

Emmanuel O. Ajani^{1,*}

¹ Department of Medical Biochemistry and Pharmacology, Kwara State University, Malete, P. M. B. 1530, Ilorin, Nigeria

Abstract: Emerging communicable diseases, such as Ebola and Coronavirus Infection Disease (COVID-19), and non-communicable diseases related to diet and lifestyle, *e.g.*, diabetes, have been increasing over the last two decades, having a great negative impact on the health services, which are already over-stretched. This again has been compounded by some largely unresolved diseases, such as malaria and HIV/AIDS, which are common parasitic and infectious diseases in many developing countries. Over several years, natural medicine has been a dependable alternative in the prevention and treatment of diseases and has been widely recognized as important for drug discovery and development. Over the world, traditional medicine has largely depended on natural products. The structural diversity and biological activity of natural products have made them a valuable source of drugs and drug leads. Several active compounds have been isolated from natural products. Among them, some follow their traditional uses while some others do not. For many years, plant's bioactive compounds, otherwise referred to as secondary metabolites, have been the source of countless compounds and leads for drug discovery. The process of drug discovery includes the identification of a lead compound, which is then proposed for drug development. Drug discovery, therefore, encompasses moving from a screening hit to a compound becoming a therapeutic agent. It is a process that requires expertise and experience. In modern drug discovery research, techniques commonly employed include combinatorial chemistry, high-throughput screening, bioinformatics, proteomics and genomics.

Keywords: Drug development, Drug discovery, Drug leads, Natural products, Plant.

1. INTRODUCTION

As the world faces global health challenges, the importance of research into drug development through natural products has become increasingly important. Plants, animals and minerals are among the natural products that have been the basis for the treatment of many diseases for centuries [1].

* Corresponding author Emmanuel O. Ajani: Department of Medical Biochemistry and Pharmacology, Kwara State University, Malete, P. M. B. 1530, Ilorin, Nigeria; E-mail: emmanuel.ajani@kwasu.edu.ng

Recently, much attention has been paid to pharmacognostic, phytochemical and pharmacological studies of traditional medicinal plants.

Medicinal plants are of vital value to the pharmacological systems since they possess multiple compounds, especially the lead molecules and thus have a number of advantages compared to synthetic molecules [2, 3]. Among natural products, plant metabolites have been revered for their usefulness as either drugs or drug precursors, being described as biosynthetic laboratories where chemical compounds could be extracted to serve multiple physiological functions [4]. Ethnopharmacological knowledge has offered a boost to the discovery and development of active and medicinally important compounds from plants. The approach is based on a body of work across several disciplines, including botany, chemistry, and pharmacology. Ethnopharmacology encompasses field observations, descriptions of the utilization and bioactivities of folk remedies, botanical identification of the plant material as well as phytochemical and pharmacological research. The study provides opportunity to explore the vast opportunities, chemical uniqueness and diversities that are present in the natural products, either as purified compounds or as crude extracts of the plant [2, 5]. The understanding of green pharmaceuticals is becoming increasingly popular and highly important as the world searches for new drugs [2]. The medicinal value of plants has come to recognition since ancient times, and available records have shown the use of many plants derived medicines for managing pathological conditions since time immemorial [6 - 8]. Literature search has shown that while some of these medicines have been used as concoctions, others have been used as crude plant extracts without the isolation of target active compounds that elicit the therapeutic function [8].

The isolation and application of bioactive plants' constituents in modern drug discovery started in the 19th century, and as of today, several active compounds with definite chemical structures have been identified in plants and are used globally as drugs [9, 10]. Compounds isolated from plants have shown some remarkable efficacy against some of the world's most challenging diseases and clinical conditions, including multi-drug resistance [11], cancer [12, 13], depressive disorders [14], diabetes [15], pest invasion [16], inflammation [17], and viral and other parasitic infections [18, 19]. The engagement of ethnobotanical and ethnopharmacological knowledge in the hunt for new medicines has offered a new route to further explore the different compounds in plants which could be important as a new class of drugs.

Despite the fact that ethnobotanical discoveries are essential factors for the development of modern medicine, globalization and urbanization have led to the disappearance of traditional medicinal plant knowledge [3, 20]. The adoption of

plants in the making of edible vaccines poses a very interesting breakthrough with respect to the constraints of traditional vaccines [21]. Edible vaccine has the potential for global immunization against diseases that have been known to be pathogenic and their concrete exploration could bring a new evolution and approach to public health and medicine [21]. The decisive role played in pharmaceuticals by plants since the prehistoric times could be further enhanced through the knowledge of phytomedicine and nanophytomedicine, and drugs could be developed from plant chemicals for specific targets in the system [22].

2. HISTORICAL USE OF PLANTS FOR PHARMACOLOGICAL PURPOSES

Life basically depends on plants as they occupy the central position in the ecosystem. The mankind has discovered the numerous benefits of the plant kingdom and has gainfully explored them not only as a source of food needed to survive but also as medicine [23]. How did man discover the therapeutic benefits of plants? Trial and errors may have acquainted man with the preparation of medicine and food from plants, and through this, he has mastered the act, built on the accumulation of experiences, and thus, is in a better position to harness the resources in his environment to meet his life needs [7, 23]. The experiences and information gathered have outlived every generation through information transmission. The evolution of the technologically driven generation, which gives prompt access to modern facilities, has brought an abundance of knowledge to human about natural resources and the use of the plant for multiple purposes [7]. Report from literature indicates that the use of plants for the treatment and prevention of diseases has its origin in the ancient Chinese, Egyptians, Indians, Greeks, Romans and the old Slavs, from where it spread across other nations of the world [23].

Traditional medicine generally describes knowledge about health, skills and practices that are peculiar to different cultures around the world, and this informs why early practices showed that there was diversity in drug development concepts [24]. Reports indicate that before the advent of the 20th century, man depended essentially on the use of crude and unpurified plants, animals and microbes' extracts for treating diseases. In the early 20th century, researchers were able to show that for medicinal activity, specific interactions occur between drug molecules and the living system [23]. This interaction is mediated by receptors which are cellular macromolecules, *i.e.*, proteins and nucleic acids. Thus, scientists have concluded that plant extracts contain chemical constituents generally referred to as bioactive compounds that elicit biological effects through interactions at target sites. In 1805, morphine, the first bioactive pharmacological compound, was isolated from opium by a German apothecary assistant Friedrich

Therapeutic Properties of Bioactive Secondary Metabolites in Essential Oil Crops

Fikisiwe C. Gebashe¹, Adeyemi O. Aremu^{2,3} and Stephen O. Amoo^{1,2,4,*}

¹ Agricultural Research Council – Vegetables, Industrial and Medicinal Plants, Pretoria, Private Bag X293, Pretoria 0001, South Africa

² Indigenous Knowledge Systems (IKS) Centre, Faculty of Natural and Agricultural Sciences, North-West University, Private Bag X2046, Mmabatho 2790, South Africa

³ School of Life Sciences, University of KwaZulu-Natal Pietermaritzburg, Private Bag X01, Scottsville 3209, South Africa

⁴ Department of Botany and Plant Biotechnology, Faculty of Science, University of Johannesburg, P.O. Box 524, Auckland Park 2006, South Africa

Abstract: Medicinal herbs and their essential oils (EOs) are of commercial and industrial importance with diverse uses as forage and fiber crops, in food, cosmetics, perfumery and chemical industries, and in traditional medicine due to their phytochemical constituents and bioactivities. This chapter was aimed at documenting the therapeutic properties of major secondary metabolites in EOs extracted from six selected economically important medicinal herbs (*Achillea millefolium* L., *Melissa officinalis* L., *Origanum majorana* L., *Pelargonium graveolens* L'Hér. *Rosmarinus officinalis* L. and *Thymus vulgaris* L.). Forty-five compounds (mainly monoterpenes) were recorded as major compounds of the six medicinal herbs. The compounds possess varying biological activities, which include antimicrobial, anti-inflammatory, antioxidant and cytotoxicity properties. Other activities reported were antinociceptive, neuroprotective effects, acetylcholinesterase inhibition, anti-ulcerogenic, DNA protection, glutathione S-transferase activity, chemoprotective, anti-depressant and sedative effects. The compounds showed potential to be used as alternative agents as drugs, cosmetic ingredients and food additives. Though some scientific evidence has confirmed the use of these herbs in various industries, much work still needs to be done to comprehend the therapeutic application of their EOs and phytoconstituents to benefit from their full potential.

Keywords: Antimicrobial, Antioxidant, Cytotoxicity, Medicinal herbs, Phytochemicals.

* **Corresponding author Stephen O. Amoo:** Agricultural Research Council – Vegetables, Industrial and Medicinal Plants, Pretoria, Private Bag X293, Pretoria 0001, South Africa, Indigenous Knowledge Systems (IKS) Centre, Faculty of Natural and Agricultural Sciences, North-West University, Private Bag X2046, Mmabatho 2790, South Africa and Department of Botany and Plant Biotechnology, Faculty of Science, University of Johannesburg, P.O. Box 524, Auckland Park 2006, South Africa; E-mail: AmooS@arc.agric.za

1. INTRODUCTION

Plants are sources of secondary metabolites with curative properties. These secondary metabolites are distributed within limited taxonomic groups and are produced by plants in their interaction with the environment for adaptation and defense [1]. They are generally responsible for specific odours, tastes, and colours in plants [2], and are sources of food additives, flavors and industrially important pharmaceuticals [3]. Most of these compounds have imperative adaptive protection against herbivores, pests and microbial infections, while some serve as attractants for pollinators and seed-dispersing animals, and as allelopathic agents [4, 5]. On the other hand, primary metabolites (such as acyl lipids, nucleotides, amino acids, and organic acids) are produced by all plants and are essential for basic life functions such as cell division and growth, respiration, and reproduction [1, 6]. Secondary metabolites are classified according to their biosynthesis pathway into phenolics and phenylpropanoids, terpenes and steroids, and alkaloids [7]. The most common pathways for the production of secondary metabolites include pentose (glycosides); shikimic acid (phenols, tannins, aromatic alkaloids); acetate – malonate (phenols, alkaloids) and mevalonic acid (terpenes, steroids, alkaloids) [8].

For centuries, secondary metabolites have been used in traditional medicine for their therapeutic properties to relieve human ailments, including chronic diseases [6]. The production of secondary metabolites in plants is greatly influenced by environmental factors such as temperature, humidity, light intensity, moisture, and mineral nutrient availability [9] as well as biotic factors. Naturally, their production is very low and dependent on the physiological and development stage of the plant [10]. Currently, there are numerous biotechnology strategies (*e.g.* plant cell, tissue and organ cultures) that have been developed to increase the production of secondary metabolites *in vitro* to meet their commercial demand [6, 10]. Secondary metabolites demonstrate numerous biological activities that stimulate their use in pharmaceutical, cosmetics, aromatherapy and nutraceutical industries. The secondary metabolites in plant extracts and essential oils (EOs) are responsible for diverse biological properties [11], such as antidepressant [12], antimicrobial [13 - 18], anti-inflammatory [19], antimutagenic [20], chemoprotectant [21, 22], antioxidant [16, 23], DNA damage protection [23] and antiviral activities [24, 25].

This chapter was aimed at providing an appraisal of the therapeutic properties of major secondary metabolites in EOs extracted from six selected economically important medicinal herbs (*Achillea millefolium* L., *Melissa officinalis* L., *Origanum majorana* L., *Pelargonium graveolens* L'Hér., *Rosmarinus officinalis*

L. and *Thymus vulgaris* L.) as a case study. The majority of the selected herbs belong to the Lamiaceae family and are of great economic and industrial importance. They are widely used in the food industry for food flavoring or as seasoning agents and are popular as perfume ingredients in cosmetics and household cleaning products [26]. In addition, they are used in traditional medicine to treat many ailments, including asthma, indigestion, headache, rheumatism [22], as tonic, antispasmodic, carminative, diaphoretic, surgical dressing for wounds, sedative-hypnotic strengthening the memory, relief of stress-induced headache [27], against colds, and in functional disorders of the circulation [28].

2. SECONDARY METABOLITES AND THEIR ROLE IN PLANTS

Secondary metabolites in plants are the active components responsible for their therapeutic properties [29]. These compounds are produced for diverse purposes, such as protection against biotic and abiotic factors [30], to counteract or in response to environmental stimuli, and to tolerate certain stress conditions [31]. Abiotic stress triggers the generation of reactive oxygen species (ROS), which alter plant metabolic processes. Consequently, excessive ROS in plants can damage plant cells through the oxidation of biological components such as nucleic acids, proteins, and lipids [32]. Although plants possess antioxidant defense capacity and repair mechanisms, oxidative damage results from the imbalance between this capacity and the rate of ROS accumulation [33].

Plants develop antioxidant defense system and produce compounds such as brassinosteroids to scavenge the excessive accumulation of harmful ROS [32]. The intrinsic antioxidant defense system consists of many enzymatic, non-enzymatic, lipophilic and hydrophilic molecules, which allow for the adaptation of plants to different environments, maintain homeostasis and detoxify ROS. The secondary metabolites sustain plants through their stress regulatory and growth-promoting activity by directly quenching or removing ROS, or by indirectly influencing hormone-mediated signaling to up-regulate defense genes. Even though there will always be a standard level of secondary metabolites in a plant produced during biosynthesis, some plant parts may contain higher concentrations of secondary metabolites at different stages of plant growth.

Secondary metabolites serve as defense compounds against bacteria, fungi, viruses, herbivores and other competing plants [34]. Additionally, some plants can use secondary metabolites for communicating with other plants by sending signals, and between plants and symbiotic microorganisms [35]. They also serve as an attractant to pollinators and seed dispersal animals; and for these reasons, they have been explored for biopharmaceutical purposes [36]. Many secondary

Bioactive Compounds as Therapeutic Intervention in Cancer Therapy

Depika Dwarka¹, Himansu Baijnath² and John Jason Mellem^{1,*}

¹ Durban University of Technology, Department of Biotechnology and Food Science, Durban, KwaZulu-Natal, South Africa

² University of KwaZulu-Natal, School of Biological Sciences, Durban, South Africa

Abstract: Neither transmittable nor communicable, painstakingly the second most fatal disease worldwide, cancer has gained the interest of scientists who are attempting with tenacity to decrypt its unknown facets, discover new diagnosis techniques, as well as to create improved and more efficient treatment methods. A major impediment to effective cancer therapy is the inability to destroy the complete malignant tumour growth and evolution of tumour resistance. Chemotherapeutic drugs are known for their cell death mode of action, thereby incapacitating non-cancerous cells in the process. A successful anti-cancer drug should kill or debilitate cancer cells without causing unnecessary damage to normal cells. Administration of natural bioactive compounds exemplifies an alternative technique as they are associated with lower toxicities. These bioactive molecules are effective and demonstrate great specificity as they possibly operate as potent anti-oxidants and apoptosis inducers. Moderating apoptosis might be helpful in managing, treating, or deterring cancer. Significantly, bioactive compounds are providing such templates. Plants have a long history in cancer treatment. More than 3000 species have been known for their anti-cancer potential. Over 60% of currently used anti-cancer agents are derived in one way or another from higher plants. This chapter describes the roles and advancements of the use of bioactive compounds in the treatment of cancer.

1. INTRODUCTION

Cancer is ranked as the second most cause of death globally. A major challenge for effective treatment of cancer is the absence of obliteration of the entire tumour cell population and the subsequent development of chemoresistance. In the past 50 years, considerable progress has been made in recognizing the molecular basis of cancer. Some anti-cancer regimens do exist, although they are linked with excessive toxicity. During the 1960s, the National Cancer Institute (USA) started to screen plant extracts with antitumor activity [1].

* Corresponding author John Jason Mellem: Durban University of Technology, Department of Biotechnology and Food Science, Durban, KwaZulu-Natal, South Africa ; E-mail: johnm@dut.ac.za

Bioactive compounds isolated from medicinal plants, as powerful foundations of new anti-cancer drugs, were found to be of growing interest from then on. Administration of these bioactive compounds in low concentrations can be fatal for microorganisms and small animals however, in larger organisms, including humans, they might explicitly alter the fastest-growing tissues like the tumours [2].

We stand at a turning point in cancer therapy. The last 60 years have been dominated by drugs, which are not limited to cancer cells. Being non-specific, these drugs also destroy normal cells and can cause serious and often deadly adverse outcomes during the process. However, the future does look promising for possible success in the struggle against cancer. As a science, the use of bioactive compounds from plants acts as an anti-oxidant and can contribute to inducing signalling pathways, including apoptosis. From many natural compounds investigated, several have been shown to be promising based on their anti-cancer effects related to apoptosis. This ultimately may lead to a greater impact on tumours specifically, thus leading to the development of successful treatment.

2. CANCER AND APOPTOSIS

2.1. Global Prevalence of Cancer

Cancer is a massive hurdle in improving the average lifespan in all countries of the globe in the 21st century. In the year 2018, an estimated 9.6 million deaths occurred due to cancer [3]. On a global scale, the collective probability of prevalence indicates that 1 in 8 men and 1 in 10 women are going to develop the illness during their lifespan. By 2050, the global burden is expected to grow to 27 million new cancer cases and 17.5 million cancer deaths [4].

Cancer morbidity and mortality rates are increasing precipitously. The common rationalizations are aging and expansion of the populace, as well as socio-economic development [5]. Environmental factors, such as tobacco use, urban development, and its associated pollution, as well as changing diet patterns, also contribute immensely to the cause of this disease. The most diagnosed cancers worldwide are lung, breast, and colorectal cancers (Fig. 1). The most common causes of cancer-causing deaths are lung, stomach, and liver cancers.

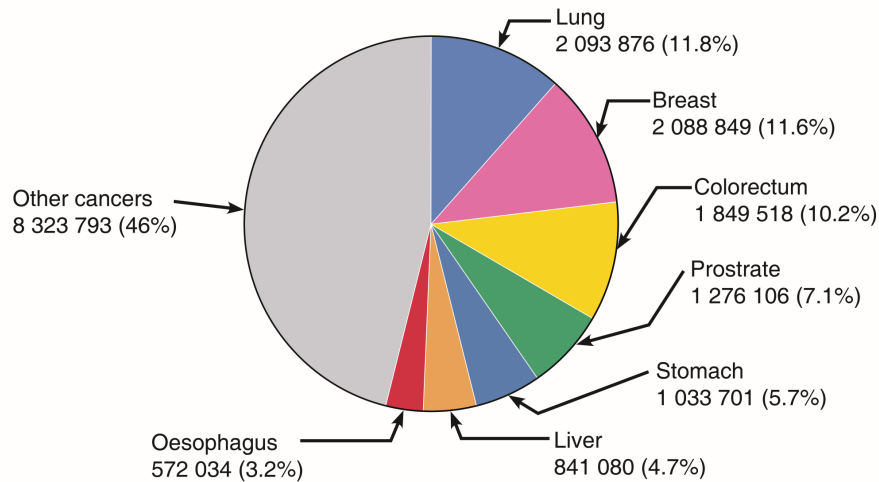


Fig. (1). The distribution of all-cancer types as well as incidence and mortality globally, for both sexes combined [3].

2.2. General Features of Cancer

Cancer is a disease in which abnormal cells divide without being regulated and can invade other tissues. This is not just one disease but many diseases. Cancer cells may spread to other components of the body through the bloodstream and lymph systems. There are more than 100 different types of cancer. Most cancers are named for the organ or type of cell in which they start.

Cancer occurs when a cell obtains adequate mutations to allow it to survive and multiply free from its normal regulation by soluble extracellular factors and by interaction with its neighbours. The genes that become deregulated are the key proteins that manage these processes. These proteins can be placed into three overlapping categories: (i) those that control signal transduction of extracellular signals regulating cell division; (ii) those that control processes associated with cell invasion; and (iii) those that affect processes associated with the cell cycle and apoptosis. In some cases, the proteins that control these processes become mutated, and they function inappropriately [2].

2.3. Pathophysiology of the Carcinogenic Process

The loss of self-controlled expansion is the enduring effect of the build-up of anomalies in various regulatory systems. This, therefore, results in alterations of cell mechanisms that differentiate cancerous cells from normal healthy cells [6]. The carcinogenic process that arises by the accumulation of mutations in these

CHAPTER 5

Bioactive Compounds as Therapeutic Intervention in Mucocutaneous Cancers

Henry A. Adeola^{1,2,*}, Rashmi Bhardwaj³, Aderonke F. Ajayi-Smith⁴, Afsareen Bano³, Tayo A. Adekiya⁵, Michael C. Ojo⁶, Raphael T. Aruleba⁷, Adeniyi C. Adeola⁸, Babatunji E. Oyinloye^{6,9} and Chinedu E. Udekwu¹⁰

¹ Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and Tygerberg Hospital, Cape Town, South Africa

² Division of Dermatology, Department of Medicine, Faculty of Health Sciences and Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

³ Centre for Medical Biotechnology, Maharshi Dayanand University, Rohtak, Haryana, India

⁴ International Centre for Genetic Engineering and Biotechnology (ICGEB), Cape Town, South Africa

⁵ Wits Advanced Drug Delivery Platform Research Unit, Department of Pharmacy and Pharmacology, School of Therapeutic Science, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, York Road, Parktown, South Africa

⁶ Department of Biochemistry and Microbiology, University of Zululand, KwaDlangezwa, South Africa

⁷ Department of Molecular and Cell Biology, Faculty of Science, University of Cape Town, Cape Town, South Africa

⁸ State Key Laboratory of Genetic Resources and Evolution, and Yunnan Laboratory of Molecular Biology of Domestic Animals, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, China

⁹ Phytomedicine, Biochemical Toxicology and Biotechnology Research Laboratories, Department of Biochemistry, Faculty of Sciences, Afe Babalola University, Ado Ekiti, Nigeria

¹⁰ Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria

Abstract: There are several beneficial effects of plant bioactive compounds in the evidence-based prevention and treatment of mucocutaneous cancers. For instance, several bioactive compounds *via* various antioxidant and immunomodulatory mechanisms have been shown to positively improve different diseases, including cancer. Considering the complex, multifactorial processes that regulate genetic and cellular function in cancer development, the use of small phytochemical molecules capable of targeting multiple carcinogenetic genes and pathways is plausible.

* Corresponding author Henry A. Adeola: Division of Dermatology, Department of Medicine, Faculty of Health Sciences and Groote Schuur Hospital, University of Cape Town, Observatory 7925, Cape Town, South Africa; E-mail: henry.adeola@uct.ac.za

Saheed Sabiu (Ed)

All rights reserved-© 2022 Bentham Science Publishers

Furthermore, the identification of molecular targets and cognate dietary bioactive molecules in mucocutaneous cancer, using applied combinatorial chemistry approaches, potentially presents a key complementary ancillary tool for developing robust, physiologically bioavailable, diversity-oriented, and cost-effective therapies. These systems biology and omics-based theragnostic tools are crucial for the management of cancers that affect the oral mucous membranes and skin in a resource-limited setting. Natural products and nutraceuticals are poised to ameliorate the burden of mucocutaneous cancers and improve the drug discovery pipelines if state-of-the-art research techniques are used to elucidate their therapeutic values in the era of precision medicine. Hence, this review focuses on the currently available and potential therapeutic benefits of plant bioactive compounds in the prevention and management of mucocutaneous cancers.

Keywords: Bioactive compounds, Mucocutaneous cancers, Oral cancer, Phytocompounds, Skin cancer, Therapy.

1. INTRODUCTION TO MUCOSAL AND SKIN CANCERS

The human surface covering (skin) adapts to the physiological demand of its local environment to either form mucosa or skin [1]. Furthermore, there are different physiological, anatomical and histological modifications of skin (*e.g.*, acral, non-acral) depending on the requisite function of the skin [2]. Even within the oral mucosa, there are functional transitions and keratinization changes [1, 3] from mucosa to the gingiva, at the muco-gingival junction [4 - 6]. The junction where skin transitions to form mucosa is known as mucocutaneous junctions [7 - 9], and has been shown to be a source of mitotically active transient amplifying cells [7]. In addition, reticular and papillary micro-vascularization networks with extensive capillary looping with the deep reticular networks have been identified as characteristic of the mucocutaneous junctions of the eyelids and lips [9]. The anatomical contiguity of skin and mucosa structures, and the spatio-physiological adaptation of the skin and mucosa structures, demand a holistic approach to a systematic understanding of its pathologies and effective personalized and targeted therapies.

A report has shown that melanoma skin cancers affect about 132,000 people globally, and non-melanoma skin cancer has an estimated incidence of *ca.* 2-3 million people every year worldwide [10]. Skin cancers are typically divided into two major groups: melanoma and non-melanoma skin cancer (NMSC). The most common NMSCs are SCC and basal BCC [11]. Other NMSCs include cutaneous lymphoma, Merkel cell carcinoma, and Kaposi's sarcoma [11]. Using available literature evidence, we discuss in this chapter the role of bioactive compounds in three common mucocutaneous cancers, *viz.*: malignant melanomas (MM), basal cell carcinomas (BCC) and squamous cell carcinomas (SCC).

1.1. Melanomas

Melanoma is a malignant melanocytic neoplasm that occurs as a result of accumulated genetic dysregulation [12]. Melanomas arise from dendritic melanocytes, which are neuroectodermal-derived cells situated in the basal layers of the skin, skin, eye, mucosal epithelial and meninges [13, 14]. Melanomas can develop from both cutaneous and mucosal surfaces [15]. Frequent melanoma sites include the head, neck, and lower extremities. Less frequent sites are oral and genital mucosa, nail beds, conjunctiva, oesophagus, nasal mucosa, vagina and leptomeninges [13].

Mucosal melanomas are tumours that arise from the melanocytes situated in the epithelia of the nasal cavity, oropharynx, gastrointestinal tract, and genitourinary tract [16]. Mucosal melanomas are uncommon and account for approximately 1.3% of all melanomas [17]. Approximately 50% of mucosal melanomas affect the head and neck region accounting for about 9% of all malignant head and neck tumours [14]. Mucosal melanomas are more aggressive than cutaneous melanomas, and approximately one-third of patients with mucosal melanoma present with advanced disease [16, 17]. Cutaneous melanoma is linked to exposure to ultraviolet light, but the anatomic location of mucosal melanoma excludes ultraviolet light exposure as a risk factor [17]. The overall 5-year survival rate is 25% despite the aggressive surgical intervention and adjuvant treatment therapies [16]. The aggressiveness of mucosal melanoma may be clarified by its late presentation and late diagnosis, vascularity of the mucous membranes, which promotes hematogenous metastases [16].

1.2. Basal Cell Carcinoma

Basal cell carcinoma (BCC) is a non-melanoma skin cancer. Approximately 80% of non-melanoma skin cancers are BCC [18], making it the most common skin cancer type globally [19]. BCCs arise from basal keratinocytes of the epidermis, hair follicles and eccrine sweat ducts [18]. BCCs are basophilic with large nuclei, and they require surrounding stroma for support during growth [18]. BCCs are usually slow-growing, and they rarely metastasise; however, delayed or inadequate treatment may lead to significant morbidity arising from destroyed skin, tissue, cartilage and bone [20]. There are five main histologic patterns of BCC: nodular, micronodular, superficial, infiltrative and morpheaform [18]. Risk factors for the development of BCC include ultraviolet radiation, immunosuppression, genetic disorders and age [19]. Most patients affected by BCC are middle-aged or the elderly [20]. Approaches for treating BCC can be surgical or non-surgical. Surgical techniques include curettage and cauterization, cryosurgery, excision and Mohs micrographic surgery [20].

Bioactive Compounds as Therapeutic Intervention in Bacterial Infections

Kazeem A. Alayande^{1,2,*}, Abdulwakeel A. Ajao³ and Mariam O. Oyedeji-Amusa³

¹ Antibiotic Resistance and Phage Biocontrol Research Group, Department of Microbiology, North-West University, Mmabatho 2745, South Africa

² Unit for Environmental Sciences and Managements, North-West University, Potchefstroom, South Africa

³ Department of Botany and Plant Biotechnology, University of Johannesburg, PO Box 524, Auckland Park 2006, Johannesburg, South Africa

Abstract: This study highlights the significance of drug resistance towards difficulties in the treatment of infectious diseases, the essence of bioactive compounds in therapeutic intervention, and the unique approach employed by bioactive compounds away from conventional synthetic drugs. Literature was gathered from different online databases to retrieve the required information. Bacterial resistance to antibiotics is a major concern that threatens clinical efforts in treating bacterial infections. This has grossly reduced clinical success on previously curable infections and/or sometimes results in a prolonged hospital stay. Antibiotics provide protection and remedy against infectious diseases. But the emergence of multi-drug resistance strains has inflicted untold loss of effectiveness on virtually every conventional antibiotic. Hence, scientific communities are propelled into seeking alternative therapies in a bid to mitigate the overwhelming consequence on public health. Bioactive molecules are important sources of newly derived therapeutic agents. They have minimal likelihood of inducing unintended immune reactions, reduced level of toxicity; are structurally diverse in nature, exhibit broad-spectrum therapeutic effects. Bioactive molecules are commonly present in small amounts in plant-based foods; and provide health benefits in addition to the basic nutritional values expected in foods. Several plant-based bioactive principles serve as inhibitors for drug resistance in order to enhance the effective delivery of the antibacterial compounds. Meat products are a good source of non-plant bioactive molecules, which are expressed in the form of peptides, vitamins, minerals and fatty acids. Other important sources include endophytic bacteria, endophytic fungi, probiotic bacteria, actinomycetes and marine organisms. Natural products are relatively

* Corresponding author Kazeem A. Alayande: Antibiotic Resistance and Phage Biocontrol Research Group, Department of Microbiology, North-West University, Mmabatho 2745, South Africa; Tel: +2763 033 3574; E-mail: jkadekunle2@gmail.com

safe when compared to their synthetic counterparts. As newly manufactured potent antibiotics become increasingly unavailable and/or unaffordable, bioactive compounds present viable alternatives. They are readily available and are derived from inexpensive raw materials *via* cheap technology.

Keywords: Alkaloids, Antimicrobials, Bacteriocins, Natural products, Phenols, Super burgs.

1. INTRODUCTION

The resurgence of multi-drug resistant bacterial pathogens of infectious diseases has significantly reduced therapeutic options in the clinics, hence propelling the scientific communities into seeking alternative therapy in a bid to mitigate the overwhelming consequence on public health. The resurgence has led to reduced clinical success on previously curable infections and in some cases, results in a prolonged stay in hospitals [1, 2]. Antibiotics, as natural or synthetic organic molecules, are lethal to microorganisms; and provide protections and remedies against infections caused by bacteria pathogens. However, the emergence of multi-drug resistance strains has inflicted untold loss of effectiveness on virtually every conventional, including the frontline, antibiotics [3].

Bioactive compounds are secondary metabolites produced by some living cells and are capable of therapeutic potentials; exhibit prophylactic and immunomodulatory activities; mitigate toxin effects; reduce oxidative stress; and enhance effective metabolism [4, 5]. Bioactive molecules are commonly present, in small amounts, in plant-based foods and provide health benefits in addition to the basic nutritional values expected in foods; hence, they are said to be non-nutrient food components that exhibit medicinal effects in living systems when ingested [6]. The presence of these molecules has been speculated to be responsible for the evidenced-based potential health benefits attributed to the adequate consumption of fruits and vegetables [7].

Moreover, there has been increasing interest in the medicinal advantages of these bioactive molecules. Plant-based foods and traditional medicinal plants employed in folklore remedies have been the primary source of these active molecules [5, 8]. Though in recent times, more considerations have equally been given to the non-plant entities, such as microorganisms and meat products, as other rich sources of bioactive agents of therapeutic importance [9]. The increasing awareness of the valuable medicinal features of the bioactive compounds has warranted the need for a collective effort among stakeholders to provide an accessible database containing required basic information on these compounds. The available public database in this respect includes USDA flavonoid content of

selected foods [10]; Phenol-Explorer: database for polyphenols in foods [11]; and EuroFIR eBASIS: Bioactive Substances in Food Information Systems [12].

Natural products have been the most important source of bioactive molecules while plants and microbes have been the centre of this for valuable drug discovery [13, 14]. Bioactive compounds are made up of extremely heterogeneous classes of compounds with structurally diverse chemical compositions and are widely distributed in nature. They have a different range of concentrations in both plants and animals; they also have specific sites of action for their biological activities and are equally effective against reactive oxygen species [15]. Meat products are a good source of non-plant bioactive molecules where they are expressed in the form of proteins/peptides, vitamins, minerals and fatty acids [16]. Other important sources include, endophytic bacterial [17], endophytic fungi [18], probiotic bacteria [2], actinomycetes [19] and marine organisms [20] (Fig. 1). Several organisms in the oceanic ecosystems are indispensable sources of natural products endowed with ranges of structural diversities and significant bioactivities for human applications [21]. The marine environment is highly rich in biological and chemical diversity. Due to the extremity, aggressiveness and competitiveness associated with the marine environment, organisms therein produce several secondary metabolites with promising potential therapeutic agents, nutritional supplements and agrochemicals [20].

Polyphenols are among the most prevalent and diverse groups of secondary metabolites, produced by plants and other organisms and are noted for their potential against quorum sensing, detoxification and formation of biofilm by pathogens [22]. Alkaloids, on the other hand, provide the underlying structures for the development of a great variety of antibiotics with a wider range of actions [23]. The bacteriocidal effect of tannins against pathogens is not limited to plasma membrane destabilization; it also involves inhibition of extracellular enzymes, disruption of metabolic pathways and blockage of the trace-nutrients required for cell growth [24]. Terpenoids are another abundant group of valuable natural products that play important roles in plant defence against pathogens and pest attacks and are widely used in pharmaceuticals for drug discoveries [25]. Moreover, saponins, due to their amphipathic property, have also been a valuable natural product employed in the development of drugs, cosmetics, and surface disinfectants against bacterial contamination, while several studies have also reported their activities against bacterial pathogens [26, 27]. The ability of some of these metabolites, and several others in their category, to modify resistance features in a pathogen provides a hedge in the combat against the spread of bacterial resistance [23].

The Use of Plant Secondary Metabolites in the Treatment of Bacterial Diseases

Pillay Charlene^{1,*}, Ramdhani Nishani² and Singh Seema³

¹ Department of Biotechnology and Food Science, Durban University of Technology, Durban, South Africa

² Council for Scientific and Industrial Research, Durban, South Africa

³ Subinite (Pty) Ltd - Godrej Consumer Products South Africa, Durban, South Africa

Abstract: Plants produce an array of secondary metabolites identified as possible anti-microbial agents that are used across the globe to treat numerous diseases and ailments. These secondary metabolites serve as unique commercial sources of various pharmaceuticals, food additives and flavouring agents, and possess diverse industrial applications. Alkaloids, flavonoids, and polyphenols are secondary metabolites shown to attack numerous gram-positive and gram negative bacteria in response to microbial infections. Secondary plant metabolites have a detrimental effect on microbial cells in several ways, such as alteration of the structure and function of the cytoplasmic membrane as well as DNA/RNA synthesis, interference with intermediary metabolism, interaction with membrane proteins, a disruption in the movement of protons leading to ion leakage, enzyme synthesis inhibition, the clotting of cytoplasmic components and interference in typical cell communication. This ultimately results in cell death. The focus of this chapter is to provide an overview of the function and benefits of plant secondary metabolites as therapeutic agents to combat pathogenic bacterial infections.

Keywords: Alkaloids, Anti-microbial agents, Bacteria, Infectious diseases, Medicinal plants, Secondary metabolites.

1. INTRODUCTION

Mankind has used several plants and their derivatives for medicinal purposes, since ancient times, especially for the treatment of infectious diseases. An excellent example of this is quinine, an alkaloid derived from the cinchona tree bark. Achan *et al.* [1] has reported on this alkaloid as a treatment for malaria and infectious diseases such as pneumonia and typhoid fever. Another wondrous anti-

* Corresponding author Pillay Charlene: Department of Biotechnology and Food Science, Durban University of Technology, Durban, South Africa; Tel: 031 373 5324; E-mail: CharleneP@dut.ac.za

microbial agent is cinnamon which is widely used in ancient Chinese medicine and has multipurpose applications due to its main biologically active agent, cinnamaldehyde [2]. There are several remedies that stem from traditional therapeutic practices which require the biological activity of various substances derived from plants to treat different diseases, including bacterial infections. Several of these traditional remedial practices are still extensively used currently. Several drugs that are currently used in medicine come from folk medicine [3].

Secondary plant metabolites, a group of biochemical substances produced by metabolic pathways of plant cells, have shown to promote the curative effects of plants. Contrary to primary metabolites, namely nucleic acids, amino acids, carbohydrates, and fats that are essential for survival, secondary metabolites are not crucial for plant growth but play a vital role in the competition between species and provide a defense against insects, herbivores, and microbes [4 - 11]. Kessler and Kalske [12] have reported that “approximately two-hundred thousand different secondary metabolites have been isolated and identified,” which were grouped in accordance with the chemical structures and/or biosynthetic pathways [13].

These secondary metabolites have been simply classified into four main groups based on their chemical structures (Table 1): terpenes (polymeric isoprene derivatives), phenolics (comprising of one or more hydroxylated aromatic ring), sulphur-containing compounds (lectins, defensins, phytoalexins and thionins) and compounds containing nitrogen (amino acids and alkaloids that lacks protein). In combination, these groups make up about 90% of all secondary metabolites [14, 15]. There are minority groups which are inclusive of saponins, lipids, essential oils, carbohydrates, and ketones [16]. Secondary metabolites are extensively used in many pharmaceutical and food industries in the production of perfumes, agrochemicals and cosmetics [3, 17]. The use of these secondary metabolites as anti-microbial agents targeting a number of pathogenic microbes is endless. Phytochemical screening of various plants has revealed several bioactive compounds such as alkaloids, flavonoids, terpenes, tannins, quinones and resins that possess antibacterial properties [18]. These could be used exclusively or as a combination to enhance the mechanism of action of conventional antibiotics. This is relevant due to the rapid emergence and dissemination of drug-resistant microorganisms [19, 20]. With the wide diversity of substances that are produced by a variety of plants, many have been discovered and studied. However, there are several that are yet to be discovered and some that are still not sufficiently studied. The antibacterial activities of many plants have been extensively researched, such as the crude extracts of basil, garlic, cinnamon, ginger, mustard and other herbs that exhibit anti-microbial properties against numerous gram-positive and gram-negative bacteria [21].

Table 1. Types of secondary metabolites of plants (adapted from Ramirez-Gomez *et al.* [22]).

Classification	Types	Example
Terpenes	Monoterpene	Geraniol
	Sesquiterpenes	Humulene
	Diterpenes	Cafestol
	Sesterpenes	Geranylarsol
	Triterpenes	Squalene
	Sesquaterpenes	Ferrugicadiol
	Tetraterpenes	Lycopenes
	Polyterpenes	Gutta-percha
Phenolics	Coumarin	Hydroxycoumarins
	Furano-coumarins	Psoralin
	Lignin	Resveratrol
	Flavonoids	Quercetin
	Isoflavonoids	Genistein
	Tanins	Tanins acid
N containing compounds	Alkaloids	Cocaine
	Cyanogenic glucosides	Dhurrin
	Non-protein amino acids	Canavanin
S containing compounds	Glutathione	-
	Glucosinolate	B-D-Glucopyrinose
	Thionins	-
	Defensins	-
	Allinin	-

There is a good chance that some novel compounds will be found that demonstrate antibacterial activities. The reason for this is that several plants use secondary metabolites as a defense mechanism against microbial pathogens. Thus, plants can partially or completely mitigate the spread of microorganisms, animal, and human pathogens [23]. Advancement in high-performance screening methods allows for the detection of novel secondary metabolites, even those from well-studied plants. In addition, genetic engineering or chemically induced synthesis are used to produce vast quantities of bioactive substances [24].

Eukaryotic organelles, the mitochondria and chloroplasts evolved from bacteria through the process of endosymbiosis [25]. These processes of endosymbiosis involve the genetic transfer of material between bacteria and the host genome

CHAPTER 8

Plant Secondary Metabolites in the Management of Degenerative Diseases

Judith N. Ohanaka^{1,*}, Uwazie C. Kenneth², Fatai O. Balogun³ and Saheed Sabiu³

¹ Department of Biochemistry, Nile University of Nigeria, Abuja, Nigeria

² Department of Biochemistry, Ladoko Akintola University of Technology, Ogbomosho, Oyo State, Nigeria

³ Department of Biotechnology and Food Science, Durban University of Technology, P.O.Box 1334, Durban 4000, South Africa

Abstract: Medicinal plants have been indispensable in the development of lead compounds for the management of human health. However, herbal remedies have not been explored maximally in modern therapeutics for the management of drug-resistant diseases, re-emerging diseases, metabolic syndrome, *etc.*

Several secondary metabolites with proven efficacious pharmacological effects have been identified from plants, some isolated but unfortunately never developed into a marketable pharmaceutical product.

Thus, this chapter provides resourceful information on the secondary metabolites of herbal plants with great pharmacological potential. Databases such as JSTOR, Science Direct, Google, PubMed, and Medline were explored for relevant information on this concept.

A spectrum of plant secondary metabolites with potent antibacterial, antiviral, antimalarial, anticancer, antidiabetic activities in different plant species were collated, the class of these metabolites and mechanism of action was compiled.

An acquaintance with efficacious secondary metabolites used in the management of various diseases will serve as a basic tool for Ethnomedical Scientists in the integration of folkloric knowledge in contemporary medicine for the formulation of herbal remedies with superior pharmacological relevance than conventional medicine.

Keywords: Antibacterial, Anticancer, Antidiabetic, Antimalarial, Antiviral, Secondary metabolites.

* Corresponding author Ohanaka N. Judith: Department of Biochemistry, Nile University of Nigeria, Abuja, Nigeria; Tel: +2348068903076; E-mail: nkechinyere.uwazie@nileuniversity.edu.ng

1. INTRODUCTION

In recent times, the improvement of health in the society has been a challenge in most countries in the world. The availability of limited resources has soft-pedaled the effectiveness, efficiency, and equity in health gains. However, the mobilization and management of societal resources to maximize success in health management are of paramount importance. Amongst the health care needs of the society; the provision of appropriate therapeutic treatment for different diseases is of paramount importance for the promotion of the well-being of the society.

Nature has been a source of medicinal agents since time immemorial. Globally, herbal drugs have been a part of the evolution of human, civilization and healthcare for thousands of years. Folklore medicine has documented the use of plants in herbal formulation for disease management. Herbal plants were prepared using common methods such as powders, poultices, tinctures, decoctions, teas, and other types of formulations [1] until the 18th century.

In the early 19th century, the evaluation of herbal plant's composition began with advances in chemical analysis and organic chemistry and this has led to the isolation/ purification and characterization of several bioactive principles. This giant stride in drug discovery led to a phenomenon of innovation in the medical field. The earliest quantum leap was the isolation of an alkaloid from the plant, *Papaver somniferum* (Opium Poppy), for the formulation of the drug, morphine, in 1805.

Later in the 19th century, several drugs were formulated from plant secondary metabolites. These include salicylic acid, the precursor of aspirin produced from *Salix alba* (Willow Bark), *Erythroxylum coca*, a primary source of cocaine- a local anaesthetic, Quinine, an antimalarial drug derived from *Cinchona officinalis*, digitoxin, a cardioactive glycoside drug synthesized from *Digitalis purpurea* and *Digitalis lanata*, and many others with clinical relevance [2].

Over the years and even in recent times, a larger number of approved drugs are originally from herbal plants and they serve as templates for synthetic modification, and pharmacological inquest and drug precursors [3]. Thus, it is imperative to state that the use of plant products for herbal drug formulation provides the bedrock to modern therapeutic sciences and validates the initiation of a verifiable system of medicine. Several benefits of using medicinal plants include its high therapeutic efficacy, little/absence of side effects, cost-effectiveness, availability, etc [4].

Currently, researchers continuously adopt approaches that explore plant for the development of new pharmaceuticals [5]. The high therapeutic value of medicinal

plants has been accorded to the presence of several active principles referred to as secondary metabolites. Thus, in this chapter, several secondary metabolites, the plant sources and mechanism of actions were highlighted to serve as a repository of information for further research that will link nature to modern disease management, thereby proffering solutions to several ailments.

The literature used for this chapter was obtained through an in-depth search of scientific databases such as Science Direct, Google, PubMed and Medline. The reports mostly cover the use of plant secondary metabolites in ameliorating/treatment of selected common ailments in folklore and modern medicine from the 19th century to date.

Seventy-nine (79) journal articles were retrieved using the keywords (Secondary metabolites, mechanism of action, anti-malarial, anti-diabetic, anti-bacterial, anti-viral, anti-cancer activities of plants) and utilized for the conceptualization of the chapter.

2. SECONDARY METABOLITES

Secondary metabolites are a group of chemical compounds produced by the plant cell through secondary metabolic pathways such as the shikimic acid and mevalonic acid pathways. These metabolites are not required for plant growth; they rather play a major role in plant interspecies competition, protection against herbivores, ultraviolet radiation, and microbes' response to abiotic and biotic stress [6]. It is also responsible for the colour, smell and flavour in plant products. Over the years, they have shown great pharmacological potential, served as sources of lead compounds with several biological activities utilized in disease management [7]. Plants' secondary metabolites could elicit therapeutic effects on humans by acting as neurotransmitters, hormones, endogenous metabolites, signalling molecules, ligands, *etc* [8]. Secondary metabolites include the diverse group of chemicals, which include alkaloids, glycosides, lipids amines, saponins, essential oils, steroids, flavonoids, carbohydrates *etc*. Currently, about two-hundred thousand different plant secondary metabolites have been isolated and identified [9].

2.1. Major Classifications of Secondary Metabolites

Secondary metabolites are simply classified into three main groups:

2.1.1. Terpenoids

Terpenoids are secondary metabolites with molecular structures made up of

Bioactive Compounds as Therapeutic Intervention in Neurodegenerative Diseases

N. Suleiman^{1,*}, I. Bulama² and L.S. Bilbis³

¹ Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, Usmanu Danfodiyo University Sokoto, Nigeria

² Department of Veterinary Physiology and Biochemistry, University of Maiduguri, Maiduguri, Nigeria

³ Department of Biochemistry, Usmanu Danfodiyo University Sokoto, Nigeria

Abstract: Neurodegenerative disorders have been implicated as the cause of many devastating diseases that are characterized by gradual loss of susceptible neurons, that are increasingly rising the prevalence of neurodegenerative diseases globally; however, therapeutics for them are lacking. There is an urgent need to develop an effective therapy that can combat the menace caused by disorders of neurodegenerative origin such as Alzheimer's and Parkinson's diseases, stroke, and traumatic brain injury. Peer-reviewed articles were explored for the purpose of this review. Several natural products from medicinal plants have been reported to have phytochemical components with bioactive effects in addition to nutritional value. An appropriate bioactive component is essential for a healthy lifestyle as it plays a significant role in the modulation of neurodegenerative diseases. This review covers the mechanism of action of neurodegenerative disorders and highlights selected classes of bioactive compounds and their effects on neurodegenerative disorders. The use of bioactive compounds in the management of neurodegenerative diseases could solve the problem of the non-availability of therapy.

Keywords: Bioactive Compounds, Disease, Intervention, Neurodegenerative, Therapeutic.

1. INTRODUCTION

Among older people worldwide, neurodegenerative disorders are a major cause of disability and premature death [1]. Among the most common neurodegenerative diseases are Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal

* Corresponding author Suleiman N.: Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, Usmanu Danfodiyo University Sokoto, Nigeria; Tel: +2348030411807; E-mail: suleiman.nasiru@udusok.edu.ng

dementia (FTD), Parkinson's disease (PD), stroke, and Huntington's disease (HD) [2]. Neurodegeneration is a component of numerous growth-related, devastating, hopeless illnesses that influence the sensory system and have become a significant danger to the strength of the old. The prevalence of neurodegenerative disease has become a global public health problem due to the ongoing aging situation facing western societies [3].

The incidence and damage of oxidants are termed as oxidative stress, and are referred to as pathogenic or etiological agents for diseases such as cancer, Alzheimer's, diabetes and aging [3, 4]. Such illnesses and evidence stimulated by oxidative stress have called for concern among scientists in finding antioxidants to prevent and treat such diseases [5]. Aging-related diseases have long been associated with oxidative stress. Continued dysfunction and death of neurons are characterized by neurodegenerative diseases. Oxidative stress is linked to mitochondrial dysfunction and endoplasmic reticulum, which causes apoptosis and disruption of protein synthesis in neurons. In neurodegenerative conditions, decreased activity of antioxidant enzymes such as catalase, SOD, glutathione, glutathione peroxidase means a decrease in the role of an antioxidant in neurodegeneration [6].

There is growing interest in antioxidants, especially, the naturally occurring type. Natural products are derived from the food, cosmetics, and pharmaceutical industries to include man-made antioxidants that are often limited owing to their carcinogenic potentials [1, 4]. Plants are a source of various secondary metabolites, many of which are natural antioxidants that can be considered sources of these substances, such as polyphenols, flavonoids, and essential oils [5].

The aim of this chapter is to report the beneficial role of bioactive compounds as the therapeutic intervention of neurodegenerative diseases. In this review, the discussion introduces bioactive compounds and its roles, separation and synthesis of bioactive compounds, applications of bioactive compounds, and pathophysiology of neurodegenerative diseases.

2. BIOACTIVE CHEMICALS

Currently, the use of medicinal plants in ancient times reflects the history of living particles. 'Bioactive chemicals' are additional nutrients commonly found in foods in small amounts [7]. Humans had no knowledge of bioactive molecules in the past, nonetheless, the use of these substances differs significantly in various ways. Natural plant chemicals are often synthesized as secondary metabolites [6]. Everyone, from a single cell to a million plant cells, makes a wide variety of survival and survival chemicals.

It is possible to break all the chemical elements of the biological system into two broad spheres. One of the main metabolites, such as amino acids, carbohydrates, lipids and proteins, are chemical substances aimed at growth and development. Other secondary metabolites, a class of chemicals that are not basic metabolites are thought to help plants improve their overall survival potential and solve environmental challenges by enabling them to interact with their environment [3].

2.1. Role and Types of Bioactive Compounds

An appropriate diet is an essential influence in a nourishing lifestyle and also plays a vital role in the inhibition of neurodegenerative diseases, including AD. The threat of dementia can be decreased by consuming a balanced diet abundant in respiratory chemicals [8]. Regardless of whether these compounds use entirely the neuro-protective impacts seen in *in-vitro* and investigations on animal species, and people under physical situations remain uncertain due to the lack of human intervention studies. There is also a lack of awareness as to whether the prices and types of chemicals contained in food make them readily available. However, their positive results have been largely confirmed by experimental studies of the epidemiological group and laboratory studies detailing the successful biological mechanisms of compound action in the mitigation of AD. Such significant improvements in selected bioactive chemicals are listed in the study. Several of these substances are in any one of the subsequent chemical categories: fat-soluble vitamins, phenolic compounds, essential fatty acids, carotenoids or isothiocyanates.

2.1.1. Phenolic Compounds

Phenolic components are present in common vegetable diets and olive oil comprising oleuropein, their most significant sources are hydroxytyrosol and oleocanthal. Oleuropein is a glycosylated seco-iridoid with several advantageous characteristics that has an important antioxidant prospect and protects nerve cells from apoptosis induced by neurotoxin [9]. It can likewise lessen the degree of A β and inhibit its production, and at the same time decrease the expression of glutamylcyclase and the enzyme involved in the synthesis of A β . Additionally, oleuropein has a metabolic effect. *Escherichia coli* cell culture *in vitro* experiment showed that Oleuropein has been shown to be immune to mutant synthesis, which rapidly binds tau protein by 67% compared to the control group [3, 7].

The efficacy of wild-type tau was 79%, whereas methylene blue, the comparison tau aggregation resistor, was 75% effective. These results propose that oleuropein can evade the production of toxic tau collections, likely owing to the combination of aldehyde groups in the forms of tautomeric of its aglycone metabolite.

Green Synthesis Application in Diabetes Therapy

Fatai O. Balogun^{1,*} and Saheed Sabiu¹

¹ Department of Biotechnology and Food Science, Durban University of Technology, P.O. Box 1334, Durban 4000, South Africa

Abstract: The use of medicinal plants and or medicinal plants-aided nanoparticles (NPs) in the management of diabetes mellitus has progressively received wider acceptance over the years due to the accompanying side effects with conventional therapy. The review explores the application of green-synthesized nanostructures in the control or management of diabetes as well as probable mechanism of NPs formation and possible toxicity. Information sourced from scientific databases including Science Direct, Google Scholar, PubMed, Web of Science, SciFinder, JSTOR revealed 58 medicinal plants explored in the synthesis of four (4) NS such as gold, silver, zinc oxide and platinum with established antidiabetic potential. The NS is characterized by varying microscopic and or spectroscopic instruments such as UV-Vis, SEM, EDS, FTIR and XRD commonly are stable, smaller-sized and mostly crystalline in nature. The functional groups responsible for the reduction and stabilization of the nanoparticles are predominantly C-O, C-H, COOH, N-H found in phenols, flavonoids, alkaloids, proteins and so on. The review identified and revealed 45% studies with less than 5% (mostly from India) conducted on animal models for antidiabetic and toxicity determinations, respectively with none for clinical studies, indicating the need for intensified efforts on research on these identified plants and unidentified species for drug development.

Keywords: Diabetes management, Characterization techniques, Functional groups, Green application, Nanoparticles, Reducing and/or stabilizing agents.

INTRODUCTION

Nanotechnology is an aspect of science involving the synthesis of materials or substances in nanometer range (between 1- 100 nm) [1] or molecular level [2]. Nanoparticles (NPs), sometimes referred to as nanostructures (NS) is an evolved field whose substantial contribution to other scientific endeavours, including pharmaceutical, medicine, bioengineering, agriculture *etc.*, is far-reaching [3] and multidisciplinary. In fact, a number of applications such as micro-optoelectronic

* Corresponding author Fatai O. Balogun: Department of Biotechnology and Food Science, Durban University of Technology, P.O. Box 1334, Durban 4000, South Africa; Tel: +27834820022; E-mail: balogunfo@yahoo.co.uk

devices, solar cells, magnetic devices, electro and photocatalytic devices, drug (gene) delivery, textile, cosmetics, x-ray imaging, biosensors, *etc.* from these domains have been generated on NPs [1, 3, 4]. Nanostructures characterized into natural or artificial are synthesized in the form of metals such as gold, silver, platinum, zinc, copper, palladium, magnetite, silicon, nickel, cobalt and or their metallic oxides and or dioxides (semiconductors), including indium oxide, ZnO, CuO, TiO₂, MgO, CaO, FeO, ZnO₂ [1, 2, 5] and or carbon, *etc.*, and they are (sometimes) ascribed to different groups based on their unique properties, hence, partly the reason for the individually exhibited unique characters and well-endowed applications. Few of the features of prominent or selected nanostructures are summarized below:

Gold (Au), among other inorganic NPs was adjudged the most effective NP [6]. This could be attributed to numerous innate properties, which include but are not limited to the ease of synthesis, biocompatibility, light-scattering ability in cellular imaging, moderate susceptibility of the chemical surface functional groups, resistance to oxidation and plasma resonance, *etc.* [7, 8]. Its relevance as antidiabetic, antioxidant, anti-inflammatory and anticancer agents have been reported [6, 9 - 11].

Silver (Ag) is another metal NP that has found its importance in many fields (medical, food, healthcare *etc.*) owing to its distinct features, including electrical, thermal, high electrical conductivity *etc.* [12, 13], which are linked to a number of applications such as antioxidative, antibacterial agents, drug delivery, antidiabetic, anticancer agents, *etc.* [14 - 16].

Platinum is one of the noble metals with high importance. It has been explored in nanotechnology and endowed with wide application in numerous scientific fields such as biological, medicine, chemical, electronics, *etc.* [17]. The antibacterial, antioxidant, anticancer and safety concerns of platinum nanoparticles have been reported [17].

Zinc oxide (ZnO), grouped with the like of graphene based on its unique importance and application is a metal oxide that has taken a prominent place in nanomedicine. ZnO, recognised to be the most important inorganic NP [18] due to the usefulness in biomedical, gas sensors, cosmetics, agriculture *etc.* [18], is reported to possess semi conducting, piezoelectric and optical properties [19] with low toxicity and biodegradable ability, *etc.* [20]. Its relevance in nano-optical devices, nanosensors, energy storage, *etc.*, has been studied by many authors [11, 19, 21].

The low toxicity and unique biological potentials exhibited by selenium (Se) placed it in the group of NPs of significance [22]. Besides, it also possesses good

absorptive capability as a result of its interactions between SeNPs and functional groups (*e.g.*, amino, carbonyl, carboxylic, cyano) of proteins [23]. It is a good antioxidative and antihyperglycaemic agent [24].

Nano-synthesis Methods

Nanoparticles have continued to be developed either by top down or bottom up approaches through physical, chemical, and biological methods. While the ‘top down’ approach involves the breaking down of bulk material into smaller particles geared at size reduction and achieved greatly through physical processes such as milling, grinding, sputtering, evaporation *etc.*, ‘bottom up’ approach is brought-about by the aggregation of the atoms or particles into nuclei and the eventual NS is achieved *via* chemical and biological processes including laser pyrolysis, sol gel process, supercritical synthesis, chemical vapour deposition, atomic condensation, co-precipitation, green synthesis, and so on [2]. The choice of a particular method in the synthesis of NPs is determined by the extent of toxicity, cost of manufacture, energy requirement, treatment necessity in terms of regulated pressure, temperature and pH, *etc.* Notwithstanding the above, the type or methods used in synthesizing these NPs and the adopted characterization techniques may partly determine the size, shape, and eventual characteristics and/or their pharmacological and/or biological potentials.

Characterization of Nanoparticles

The synthesis of the nanoparticles is accompanied by arrays of spectrometric and microscopic techniques such as ultraviolet-visible (UV-Vis), fourier-transform infrared (FTIR), transmission electron (TEM) or scanning electron (SEM) or fields emission scanning electron (FE-SEM), x-ray diffraction (XRD), dynamic light scattering (DLS), energy dispersive (EDS), differential centrifugal sedimentation (DCS), *etc.*, which determines the point of maximum absorption and or the band gap energy, depicts the type of size (from as small as 5 nm to as big as >500 nm), shapes (cubical, spherical, triangular, irregular, pyramidal, hexagonal, octahedral, decahedral *etc.*), morphology (crystalline, amorphous, *etc.*), stability, homogeneity, surface area, and so on. The characterization aspect is germane to afford information on the system and control of the NPs [1].

Green Synthesis of Nanoparticles

Green nanotechnology is an evolving application that combines green chemistry and engineering [25] fields focusing on the reduction of energy consumption and the use of cost effective materials to produce ecofriendly materials. This type of synthesis falls into the biological method of NP synthesis using various biological substances, including enzymes, microorganisms (fungi, bacteria, algae), yeast,

CHAPTER 11**An Update on Green Synthesis Application in Cancer Therapy****Karishma Singh¹ and Saheed Sabiu^{1,*}**¹ *Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, P.O. Box 1334, Durban, 4000, South Africa*

Abstract: Cancer is one of the most common health problems affecting the human population globally. One of the major focus areas that bio-nanotechnology is taking nowadays relates to nanomedicine and the use of nanomaterials in cancer therapy. Furthermore, the green synthesis of nanoparticles has been described as an effective, inexpensive, and environmentally friendly procedure. Biological organisms such as bacteria, fungi, cyanobacteria, algae, plant extracts, and enzymes and biomolecules have been reported to successfully synthesize metal nanoparticles. This review describes the types of green synthesized nanoparticles, the different green synthesis methods of nanoparticles, and their application against various cancer cell lines. Although the plant-mediated silver nanoparticle synthesis appeared to be the most common green synthesis approach used in cancer therapy, gold nanoparticles are postulated to be a better, more efficient alternative, whilst the use of zinc oxide nanoparticles is becoming an emerging trend. This review concludes that metal nanoparticles can be used as potential anticancer agents.

Keywords: Biomolecules, Cancer therapy, Drug-delivery, Metal nanoparticles, Microorganisms, Plant extracts.

1. INTRODUCTION

Nanotechnology has become a fast-growing field in the world of science and technology in recent times due to its multiple applications [1, 2]. It can be applied across a variety of fields such as optics, electronics, catalysis, biomedicine, energy science, mechanics, and the cosmetology and pharmacology industry [1, 3]. The word “nano” is of the Greek-origin, meaning extremely small; hence, nanoparticles are characterized as being relatively small in size (1-100 nm) and having an increased surface area to volume ratio [3, 4]. Generally, nanoparticles

* **Corresponding author Saheed Sabiu:** Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, P.O. Box 1334, Durban, 4000, South Africa; Tel: +2731 373 5330; E-mail: sabius@dut.ac.za

differ greatly in shapes (spherical, rod, and triangular) and sizes, and for the metal nanoparticles, for instance, their shapes have been reported to significantly influence their optical and electronic properties [5, 6]. The size of nanoparticles varies according to the field of application. For instance, in medicine and pharmaceutical sciences, nanoparticles synthesized for therapeutic drug delivery are often larger than 100 nm to accommodate an adequate quantity of drugs to be delivered to target tissues or organs [7, 8]. Specifically, for cancer therapy, the desired size of the nanoparticles ranges between 70–150 nm as the arrangements in the endothelium in a developing tumour is about 100–780 nm [6]. To date, the metal nanoparticles for cancer therapy have remained a viable alternative to the conventional anticancer drugs (chemotherapy) and treatments (laser therapy, and surgery targeting tumour cells) due to several side effects such as weight loss, anemia, hair loss, fatigue, bleeding and bruising, appetite loss, diarrhea, blurred vision [7, 9]. Comparatively, cancer nanoparticle therapies, particularly those from biological sources, have been reported to be less toxic, more reliable, economical, environmentally friendly, and effective [1, 6]. Consequently, the bioscience has been employed as a potential weapon in cancer therapy.

The ultimate goal of nanoparticles is to diagnose cancer at an early stage and deliver the therapeutic agents (drugs) at an optimum dose to the right target to kill the cancerous cells. Conventional methods such as chemotherapy and radiotherapy are known for their harsh side effects and often target cells that are not specifically cancerous, resulting in the elimination of healthy cells [9]. Moreover, numerous problems in toxicity, inactivity, and limited bioassay are inferred from the weak pharmacokinetic effects of cancer medications resulting from lower solubility, stability, and metabolism. Therefore, effective formulations must be established that can address these difficulties and selectively target tumor sites without compromising the viability of healthy cells and tissues. Understanding the precise mechanism of metal nanoparticles as potential anticancer agents is also imperative. Here, various metal nanoparticles, as well as green synthesis and characterization methods, are discussed to offer an innovative possibility to examine biological units for nanoparticle synthesis and to evaluate their possible effects on cancer therapy.

2. GREEN SYNTHESIZED NANOPARTICLES IN CANCER THERAPY

Nanoparticles are desired for biomedical applications because they are essentially a bridge the gap between bulk materials and atomic or molecular structures with unique mechanistic, optic, and biology-related attributes [10, 11]. Each nanoparticle has a significant contribution to green synthesis applications. Nevertheless, metal nanoparticles are emerging as a preferred choice over

conventional therapy and are being widely used in therapeutics [7, 12, 13]. Of the metals (silver, gold, zinc, nickel, iron, selenium, palladium, copper, and platinum, *etc.*) used in nanoparticle synthesis, those from silver, gold, and zinc have extensive and promising applications in cancer therapy. Hence, this section briefly highlights silver, gold, and zinc nanoparticles in both effective cancer diagnosis and therapy [8].

2.1. Silver

Silver is the most desired metal for nanoparticle synthesis due to its unique morphologies, stability, and controlled geometry [4, 14]. Silver nanoparticles (AgNPs) can be synthesized using either plant extracts or various microorganisms [6] and are being designated as most effective in the biomedical field because of their numerous applications [2, 15]. Besides their effective anti-cancer applications, studies have also implicated AgNPs as anti-parasitic, anti-septic, antimicrobial, anti-inflammatory, anti-diabetic, anticancer, and antioxidant agents [3, 5, 15 - 17]. The anticancer activities of AgNPs have been analyzed and reported against a range of cancer cells such as breast cancer, lung cancer, ovarian cancer, and human hepatoma cells *in vitro* [7]. Rattan *et al.* [18] have also reported the anticancer activity of 23 plant extracts used to synthesize AgNPs and lent credence to their being potent anticancer drug-delivery systems.

2.2. Gold

Gold is another metal that is also known to be compatible with biological material. Gold nanoparticles (AuNPs) are some of the most widely studied nanoparticles because of their surface plasmon resonance (SPR) and optical properties [15]. AuNPs can easily be synthesized, have high chemical and thermal stability, low cytotoxicity and show intense surface SPR, and can be used as drug carriers [15]. Gold nanoparticles can be prepared in a varying range of core sizes (1 to 150 nm), making it easier to control their dispersion [19]. They have a broad application range in biomedicine, such as biomolecular immobilization, leukemia therapy, antimalarial and anti-arthritis treatment, and biosensor design [20]. Furthermore, the ability of AuNPs to bind ligands (antibodies, peptides, and nucleotides) by interacting with their amine and thiols groups provides a suitable means of producing specified biomarkers and conjugating therapeutic agents [21].

The biocompatibility of soft bases like thiols and their strong interactions make it possible for AuNPs to be essential in cancer therapy [2, 21]. Due to the capability of AuNPs to inhibit proliferation induced by vascular endothelial growth factor (VEGF), they have been used to treat ovarian cancer and metastasis attributable to VEGF [22]. This submission has been substantiated *in vivo* by Bhattacharya and Mukherjee [23] in a Mouse Ovarian Tumour Model (MOT). The study found that

CHAPTER 12**Oxidative Stress Involvement in Antibacterial Therapy****Christiana E. Aruwa¹ and Saheed Sabiu^{1,*}**¹ *Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, P.O. Box 1334, Durban 4000, South Africa*

Abstract: Antimicrobial therapy is necessary to reduce the global burden of disease and infection. Oxidative stress (OS) may play a key function in determining the extent of efficacy of antimicrobial treatment regimens. However, whether the agent has a ‘static’ (inhibitory) or ‘cidal’ (killing) effect or the ability to induce an oxidative state, achieving therapy is a complex one. Bactericidal agents are known to induce a downstream cascade of responses in bacteria beyond their direct target(s). These responses correspond with the generation of reactive oxygen species (ROS) and the development of OS that eventually results in the disruption/destruction of integral components and/or processes within bacteria cells. In contrast, bacteriostatic antibiotics may not always induce cell death. Both classes of antimicrobials are useful in antibacterial therapy. The actualization of an oxidatively stressed microbial cell is key to optimizing the available antibiotic therapy options for efficient treatment and reducing the acquisition of microbial resistance. Studies are still required to expatiate on the role played by OS in antimicrobial therapy. This chapter, therefore, focuses on discussing available research data and knowledge on this complex role by OS, while highlighting potential future application and development prospects. In addition, the chapter touched OS and their sources, antimicrobial lethality-OS association, factors affecting OS-mediating therapy and efficacy, bacterial adaptations to OS in response to antimicrobial treatment and prospects for combination therapy with bactericidal agents and adjuvants.

Keywords: Oxidative stress, Reactive species, Antibiotics, Antimicrobial therapy, Bacteria, Adaptations.

1. INTRODUCTION

Antimicrobials-induced cell apoptosis is a multifaceted and complex process [1, 2]. While more effort has been directed towards the derivation or discovery of

* **Corresponding author Saheed Sabiu:** Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, P.O. Box 1334, Durban, 4000, South Africa; Tel: +2731 373 5330; E-mail: sabius@dut.ac.za

new antimicrobials and their specific target(s) in microbial cells, this approach is simplistic. This approach points to the view that antimicrobials evince their effects through the inhibition of specified targets only. However, the upgrades in high-throughput techniques have empowered scientific analysis into microbial responses to stress or toxic conditions [3]. In other words, microbial cell death or inhibition could be a function of more than the antibiotic-target specific theory. It may also be a consequence of affected cell processes, for example, physiological and metabolic processes, as well as interactions that transcend cell target(s), and may be associated with the development of oxidative stress (OS) in cells under treatment conditions [3]. The accumulation and excessive presence of reactive oxygen species (ROS) in a living system could culminate in oxidative stress (OS). Oxidative stress has also been defined as a state of antioxidant deficiency [4]. ROS usually target lipids, proteins, RNA and DNA [5], and their occurrence beyond optimal level is harmful to cells [6].

Generally, antimicrobial therapy faces pertinent challenges on a global scale, given the increase in antimicrobial resistance (AMR) of microbial species to available antibiotics or antimicrobial agents [7]. In a bid to tackle AMR, research should not be limited to the discovery or synthesis of novel antimicrobials and new modes of action but also extended to investigations on integral factors that contribute to the development of AMR and antimicrobial tolerance [7]. Under certain conditions, exposure of bacterial cells to some classes of antimicrobials could enhance increased production of ROS, that may cause death and disruption of the target with which the drug or agent interacts within the cells [3]. In contrast, antioxidants and OS defences could contribute to reducing susceptibility to antibiotics and be involved in bacterial responses to antibacterial or antimicrobial agents [7].

Antibacterial agents, especially bactericidal antibiotics, disrupt the bacterial cells they permeate and may cause irreversible damage or death to the cells through breakage in deoxyribonucleic acid (DNA), and induction of oxidative stress biomarkers. These effects are, however more pronounced in bactericidal agents [8, 9]. In the Fenton pathway, DNA is damaged by hydrogen peroxide (H_2O_2), a ROS [10]. It has also been reported that aerobic microbial species such as *Escherichia coli* produce significant quantities of intracellular peroxide to induce OS and cause damage to their own DNA [11].

Again, in the study of the *E. coli* metabolome, some changes were profiled in response to three antibacterial agents, that is, quinolones, aminoglycosides, and β -lactams antibiotics. *Escherichia coli* cells showed a decrease in lipid quantities, breaks in the nucleotide chain, an increase in the redox condition within cells, and upregulated levels of central carbon metabolites [12, 13]. The loss of homeostasis

in the cell's metabolic state led to toxic shifts which was an evidence of OS in treated cells. Following the establishment of an oxidatively stressed state, breakage in DNA, increase in nucleotide oxidation, malondialdehyde adducts, and carbonylation of protein were also reported [8]. Hence, shifts in cell metabolism may function in the regulation of bacterial susceptibility responses [14, 15]. The disturbance of metabolic processes has been reported to stall the uptake of antibiotics [16] and induce bacterial protection by decreasing cell growth [13]. It may also downregulate the generation of by-products which are toxic to the cells [3]. Thus, microbial reactions to antibiotics used in antimicrobial treatment can be a function of several interactions that induce a stressed oxidative state in affected cells.

Considering the foregoing, increasing research insights into how antimicrobial agents impact microbial physiological and metabolic responses, as well as the OS-bacterial cell disruption link in antimicrobial therapy, could also be key to solving the nagging global challenge of AMR. This would further aid the evolution of therapeutic techniques to improve the efficacy of treatment regimens in the future. This chapter, therefore, aims to synergize a range of relevant and available information in the literature on the OS function in antibacterial therapy. Information for the chapter was derived from research and review articles and an array of online databases.

2. DISCUSSION

2.1. Sources of Oxidative Stress

Some of the known sources of oxidative stress include, but are not limited to obesity or metabolic syndrome, leukocytospermia, alcohol and tobacco usage, bacterial prostatitis; sexually transmitted disease (STDs), for example, those caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae* (Gonorrhoea), and *Treponema pallidum* (Syphilis); viral infections like hepatitis, human immunodeficiency virus (HIV), mutations that occur in microorganisms which increase OS stress levels [4], and antimicrobial agents used in antimicrobial therapy. However, the effects of ROS generation leading to oxidative stress as a mechanism of antibacterial action, the OS-antibacterial lethality link in antimicrobial chemotherapy, and bacterial mutations in response to OS and antibacterial agents are the subjects of focus.

2.2. Mechanism of Action of Antibacterial Agents

Some antibacterial agents that have shown ROS-generating capacity as a mode of

Phytotherapy and the ‘Omics Concept

Ismaila O. Nurain^{1,*}

¹ Department of Pharmacology, the University of Minnesota Medical School, Minneapolis, USA

Abstract: Medicinal plants are particularly important biobanks for chemical and structural diversity and the identification and characterization of druggable agents in the pharmaceutical developmental processes. Many researchers are now striving to upgrade traditional medicine to match modern medicine. One of the greatest means to do this is by omics sciences. This chapter focuses on the description of ‘omics technologies as a pivotal tool in the standardization and modernization of phytotherapy. Some of the ‘omics approaches discussed are genomics, proteomics, chemoproteomics, glycoproteomics, immunoproteomics, interactomics, transcriptomics, metabolomics, toxicogenomics, pharmacogenomics, pharmacometabolomics, phytochemomics, toxicometabolomics, phenomics, cytomics, and metallomics. These fields of sciences are very important for the understanding of components and mechanisms of actions of cells, tissues, organs, and systems with disease mechanisms. Thus, ‘omics sciences have been gaining ground and acceptance in the drug development processes of modern medicine and as a precision medicine for disease management. Overall, utilizing ‘omics technologies as tools for the standardization and modernization of phytotherapy is a promising way to improve traditional medicine in tackling several life-threatening and deadly diseases.

Keywords: Phytotherapy, Medicinal plant, Omics technology, Genomics, Transcriptomics, Proteomics, Metabolomics.

1. INTRODUCTION

The study of the use of plant extracts or extracts from another natural origin as therapeutic agents that promote the healthy living of organisms is referred to as phytotherapy or herbal therapy. It involves the use of the whole plant or parts of the plant as foods, teas, powdered herbs, liquid extracts, incense, smudges, and skin preparations to manage organisms’ conditions. Examples are adaptogens, adjuvants, analgesic, antiemetics, aperients, astringents, *etc.* Adaptogens are herbs

* Corresponding author Ismaila O. Nurain: Department of Pharmacology, the University of Minnesota Medical School, Minneapolis, USA; Tel: +2348068088828; E-mail: isnurain@gmail.com

that are used for the improvement of the adaptability of the body to stress. Adjuvants enhance the body's response to a remedy. Also, analgesic and anodynes plants are used for pain relief in the same manners and antiemetics are used for lessening nausea and preventing vomiting. Aperients are mostly used as moderate laxative and digestion or appetite modifiers. Astringents could be used in tissue contraction and regulation of body secretion. They are also used to tighten or change the tone of the body. To mitigate or soothe inflammation, Balsamic herbs are extremely useful. Other uses of plants and plant extracts are as an expectorant, emmenagogue, hypnotics, and demulcent to mention a few. Currently, it has been reported that 38% of United States adults depend on some kind of herbal medicine as part of their alternative medicine. Being that as it is, there are a lot of concerns on their effects in the general biological system, toxicological effects, efficacy, and reproducible method of preparations, *etc.*

Historically, phytotherapy as a way of disease management is as old as the age of man on earth. The first man to use the term "phytotherapy" as a concept in 1913 was Henri Leclerc, who was a French physician. Since the beginning of the world, there was always quest to search for the rescue for human discomfort or disease. The act of using medicinal plants for different human conditions (disease states or discomfort of any form) is natural [1]. Moreover every knowledge about herbs was gained by experience. The reason for using a particular plant or plant product would be as a result of other user experiences and that was how thousands of plants become known for their roles and functions in biological system. One of the written evidence of the use of herbal therapy was found in Nagpur with a Sumerian Clay Slab about 5000 years old. It has more than 250 different plant components made up of 12 different recipes [2]. "Pen T'Sao" was written by Emperor Shen Nung circa 2500 BC. In the book, about 365 drugs were proposed from dried plants' parts. Some of these prescriptions are still in use today e.g., *podophyllum*, *Rhei rhizoma*, camphor, *Theae folium*, cinnamon bark, ginseng, jimson weed, gentian *etc* [3, 4]. In India, a book, "Vedas" described the most abundant plants for disease treatment. It is established that most numerous spice plants used until today originated from India e.g., pepper, nutmeg, clove. *etc* [5]. Also, in 1550 BC, about 700 different plant species such as willow, fig, juniper, onion, common centaury, aloe, castor oil pomegranate to mention, but few were gathered and enumerated for the bioactivity potentials [6, 7]. Other historical information about the use of herbal medicine can be found in the literature [8 - 13].

As mention above, the use of phytotherapy in the management of different diseases has been existent for centuries. Many researchers have worked on the cytotoxicity effects of several medicinal plants in the efforts to provide a cure for cancer disease. Wargovich and co-workers have reported the effect of herbs in the

prevention of cancer and other diseases [14]. For prostate cancer, *Pygeum africanum*, which is commonly used in Europe and the USA for benign prostatic hypertrophy (BPH), has been proven to be very efficacious against cancer and safe for consumption at the described dosage [15]. Thus, this plant could be a good supplement for the prevention of prostate cancer. In another research *Boophone disticha*, a South African ethnomedicinal plant, was investigated phytochemically and phytotherapeutically for its usage in the management of diseases such as inflammatory disease, mental illness, and wounds healing [16]. Also, phytochemical analysis of *Genus uncaria* was carried out on nineteen species of the plant, which revealed some important pharmacological properties, including usage for rheumatism, hyperpyrexia, asthma, hypertension, *etc.*, in South America, Malaysia, Africa, Philippines, and China [17]. Other applications of phytotherapy in diseases' management have been enumerated, such as liver disease [18, 19], skin disease [20], Alzheimer's disease [21], urologic disease [22], nonsurgical treatment of periodontal disease [23], Parkinson's disease [24], cardiovascular disease [25] coronavirus [26, 27], urinary stone disease [28], and cancer [29].

The different kinds of phytomedicines used in the management of various conditions are also referred to as phytotherapy. The combined approach to bridge phytotherapy and modern medicine and between available genomic information and several biological processes involve the use of the different strategies from many analytical strata in combination with sophisticated computational studies [30, 31]. Although the genomic study is very significant and impactful, it is imperative to fill the gap between the series of information for the identification and characterization of probable biomarkers with the physiological and pathological processes in the living system coupled with potential therapeutic agents [32]. The field of science responsible for this is omics science. It is relevant in the standardization and characterization of phytomedicine with correlation to genomic information. An omics concept is a vital technique in the modernization of phytotherapy. It involves technologies that measure some characteristic of a large family of cellular molecules, such as genes, proteins, or small metabolites. It is a branch of science comprised of many disciplines in biological sciences with their names ending in omics such as genomics, proteomics, transcriptomics, metabolomics, glycomics, lipidomics. It involves the characterization and quantification of structure, function, and dynamism which make up the organism. As a concept, omics science is commonly used by research and medical professionals like bioinformaticians and molecular biologists. The importance of the application of omics in phytotherapy cannot be overemphasized since it has penetrated almost all aspects of medicine.

Omics can be considered as a basis for precision medicine. The results of the data

Phytoinformatics in Disease Management

Ismaila O. Nurain^{1,*}

¹ Department of Pharmacology, the University of Minnesota Medical School, Minneapolis, USA

Abstract: The profound importance of medicinal plants as therapeutic agents as well as their economic values has captured the attention of researchers around the world. However, it has been recognized that standardization of medicinal plant research is required for its incorporation into modern medicine and to maintain the healthy development of the traditional medicine industry. Due to this fact, several extensive research efforts have been added to the existing approaches to upgrade the sector through standardization and authentication of medicinal plant and plant products as well as bioengineering of metabolic pathways. This chapter has divulged information about the application of computational omics approaches to medicinal plant research and its relevance in disease management. Omics studies such as genomics, transcriptomics, proteomics, metabolomics as well as multi-omics data integration were accounted for their application in a medicinal plant. Some bioinformatics programs, tools, and web databases were explained and their application in the phytoinformatics analysis of medicinal plant was discussed. This chapter concluded with the importance of storing, integrating, and management of biological and medicinal plant data to make them available as information used in disease management. It is, therefore, hoped that this chapter will enlighten medicinal plant researchers more on the availability of computational tools to use in standardizing traditional medicine and authenticate the methodologies by making them reproducible and applicable to disease management.

Keywords: Omics studies, Medicinal plants, Bioinformatics tools, Databases, Standardization, Plant metabolites, Disease management.

1. INTRODUCTION

Every living organism is bound to pass through both healthy and disease states at certain times in its life span. The change in the biological system from healthy to disease state quest for remedy, and this gingers the search for various sources of traditional medicines. The use of plants and plant products as remedies for human diseases dates back to time immemorial. The recognition of medicinal plants as a vital source of remedies for several human diseases came into play when modern

* Corresponding author Ismaila O. Nurain: Department of Pharmacology, the University of Minnesota Medical School, Minneapolis, USA; Tel: +2348068088828; E-mail: isnurain@gmail.com

medicine practitioners started questioning the safety, standardization, reproducibility of methods, and authenticity of traditionally based remedies [1]. Even though it cannot be disproved that medicinal plants are efficacious, some questions could not be answered. However, with time, the introduction of sciences into traditional medicine enlighten the dark spot in the use of ethnomedicinal plants to treat human diseases. Tradition medicine is common in Africa, India, China, Arab and other countries with western countries accepting it later after some facts have been established regarding the potency and safety of plants [2, 3]. Thus, the world depends on medicinal plants for the management of disease and other unhealthy states. The allopathic, which is widely accepted nowadays, is also based on medicines from the animal source, plants origin, and mineral resources. Medicinal plants are renewables reservoirs, safe for consumption, readily available, and cheap [4, 5]. Medicinal plants are good sources of useful chemicals with bioactive properties and so they are the most acceptable sources of drug and therapeutic agents in traditional medicines, complementary and alternative medicine, and also in the allopathic system of medicines [6]. Several ethnomedicinal plants have been proved efficacious in the management of many diseases such as neurodegenerative diseases [7], inflammatory and cardiovascular diseases [8], HIV/AIDS [9], plants' diseases [10 - 12], sickle cell disease [13, 14], cancer [15], and infectious diseases [16 - 18].

Even though medicinal plants are particularly important sources of therapeutic agents used by humans for ages, the knowledge of the vital information about the molecular, chemical, and cellular systems is just gaining ground with the invention of modern technologies and molecular biology techniques, jointly referred to as omics sciences. The advent of omics sciences enables scientists and researchers to explain complex information in genes and genomes coupled with metabolic proteins involved in biological systems [19]. Currently, in all the continents, medicinal plants have provided substantial advantages to the pharmaceutical industry in the same ways as they have provided stability to the biomedicine industry. This was possible through the establishment of pressing and urgently standardized and advanced research activities on the medicinal plants. So, in disease management, there is a need for phytochemical informatics to decipher and understand the biomarkers and bioactivities of phytochemicals. Two tasks in the applications of phytoinformatics to medicinal plant research in disease management are to provide standardization and characterization of the plant materials as well as to decipher the mechanistic annotations of the metabolic pathways of the plants' bioactivities. These applications of phytoinformatics would be accomplished through medicinal plant research using multi-omics data integration and technologies such as genomics, proteomics, transcriptomics, *etc* [20, 21]. On the other hand, phytoinformatics is combined with system biology to bridge the gap between the phytochemical information, their bioactivities, and

disease management. The system biology approach is a multidisciplinary way to understand the complex processes in the human biological system. It is the combined efforts of chemists, biologists, physicists, mathematicians, and bioengineers to integrate an enormous amount of data from omics studies to arrive at a precise medicine for a disease. Reports have indicated the importance of system biology in the understanding of the regulatory and metabolic pathways networks in plants [22 - 24]. But what is disease management? The concept of cost reduction and improved life quality of individuals living with disease through total prevention, cure, and integrated care from professionals is referred to as disease management. Disease management is the way of a regulated and coordinated intervention program for the health sector. So, to be able to outline proper and accurate disease management, there is a need for integrated information from genomics, proteomics, transcriptomics, metabolomics, and other omics science to identify, characterize, and validate the targeted disease biomarkers as well bioactive ingredients from medicinal plants.

This chapter is aimed at deciphering and elucidating the phytoinformatics concept in disease management. It will include the relevance of medicinal plants in disease management, informatics from omics sciences and their relevance in disease management, phyto-bioactive chemical data integration from different databases, tools, and some computational and bioinformatics analyses to integrate Phyto-bioactive chemical data for disease management. The chapter will be concluded with further and prospective areas to be explored by the traditional medicine researchers in the phytoinformatics for increasing the standardization of the medicinal plant plant-based diseases management.

2. RELEVANCE OF MEDICINAL PLANTS IN DISEASE MANAGEMENT

In the quest for the efficacious, safe, cheap, and readily available cure and treatment for various human diseases, the human being has explored several other organismal species including plant and plant-related species. The ethnomedicinal plant has been the most important and reliable source compared to other sources of human cure and treatment; they possess various secondary and primary metabolites required by the living organisms and metabolic pathways that make up the organism [25, 26]. The metabolites modulate the pathways or cause biochemical changes that could help in the treatment of diseases. Moreover, for every plant identified for its bioactive chemicals, all parts of the plant are particularly useful. These include the fruits, seed, leaf, bark, stem, roots, flowers, all prepared in different forms depending on the diseases and method of development [27].

The use of the plant as a remedy dated back to the prehistoric era. Not only that

Computational Applications in the Drug Discovery and Development Processes

M.O. Kaka¹, J.O. Aribisala², S. Karishma², A.K. Oyebamiji³, T.A. Ajayeoba¹, N.J. Ohanaka⁴ and S. Sabiu^{2*}

¹ Department of Microbiology, Adeleke University, Ede, Osun State, Nigeria

² Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, South Africa

³ Computational Chemistry Research Laboratory, Department of Pure and Applied Chemistry, Ladoko Akintola University of Technology, Ogbomoso, Oyo State, Nigeria

⁴ Department of Biochemistry, Nile University of Nigeria, Abuja, Nigeria

Abstract: The traditional drug discovery and development process has been shown to be not only time-consuming and risky, but also expensive. The identification of disease-related targets, the identification and optimization of novel leads, and drug development are the three critical steps in modern drug discovery. Approaches such as genomics, proteomics, molecular biology, cell biology, structure biology, computational biology, and bioinformatics are commonly used to identify disease-related targets. Here, we appraised the significance of computational applications in modern drug discovery and development. It was revealed that the adoption of novel computational technologies has proven to be efficient in identifying drug targets and drug candidates against degenerative diseases such as diabetes, cancer and bacterial infections, and the concept holds significant promise for a future breakthrough in drugs discovery, design and development. The challenges involved with computational applications in drug discovery are basically those of precision and accuracy in handler and software limitations. However, future breakthroughs and effective outcomes depend on the combination of advanced models with vast experience in the field of drug discovery and an understanding of the limitations of the existing computational tools.

Keywords: Bioinformatics, Computational Science, Drug Discovery, Drug Development, Life Sciences, Therapeutic Target.

* **Corresponding author S. Sabiu:** Department of Biotechnology and Food Science, Faculty of Applied Sciences, Durban University of Technology, South Africa; Tel: +2731 373 5330; E-mail: sabius@dut.ac.za

1. INTRODUCTION

Historically, medicines have often been derived from fungi, herbs, plants and other natural sources known to man [1]; the naturally derived drugs constituted those of plant, animal, and microbiological sources. Many important drugs were derived from plants, both directly and indirectly- hence, plants were deemed to be vital sources of novel pharmacologically active compounds [2]. Until the mid 19th century, there was little to no scientific understanding of why certain substances (mostly natural products) produced medicinal effects. There was also a non-existent use of man-made/synthetic drugs for disease cure. Basically, pharmaceutical drug discovery trended through a different era and commenced with the discovery of the first synthetic compound (chloral hydrate) in 1832, which was not used medically until 1969. Drug discovery from synthetic compounds of organic molecules such as citric, gallic, malic, lactic, oxalic and uric acids was rampant [3]. In the 20th century, fusion of knowledge from biochemistry, microbiology and synthetic organic chemistry yielded the production of natural, semi-synthetic, and synthetic drugs, whereas the discovery of antibiotics by Alexander Fleming aided the development of more antibiotics in order to treat infectious diseases [4]. Further advances in drugs discovery, design and development took place with the discovery of vaccines, active modified purines as anticancer drugs, and antiviral drugs [5, 6], which were greatly helped by the discovery and the knowledge of DNA Recombinant Technology. In the 21st century, multidisciplinary approaches, bioinformatics, combination chemistry and molecular modeling have aided pharmaceutical advances in drugs design and development [7].

In modern day trends, drugs discovery occurs through gaining new insights into a disease process, allowing the design of an agent(s) that stops or reverses the effects of the disease [8]. Drugs are also discovered when many tests of molecular compounds are carried out in order to observe their effects against certain diseases (Fig. 1). The discovery of new drugs also stems from the knowledge of existing treatments that have unanticipated effects and furthermore, new technologies, these include technologies which work in the manipulation of genetic material and those that function in the specific targeting of drugs/medical products to body sites [9].

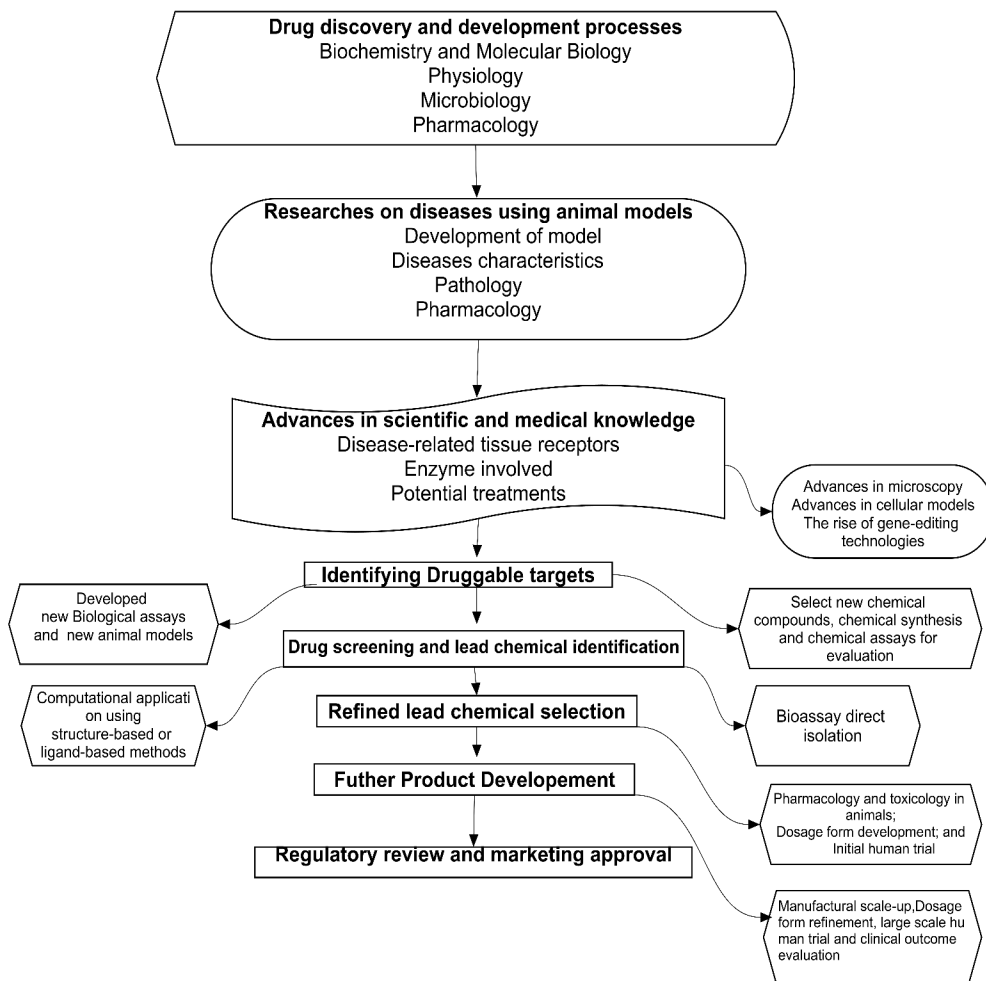


Fig. (1). Flow Chart of Drug Discovery and Development.

After identifying promising/lead compounds, experiments are carried out in the development of new drugs (Fig. 1) to gather information on the drug's absorption, distribution, metabolism, and excretion [10]. The potential benefits of the new drug in addition to its mechanisms of action and the best dosage for effective use, are also examined. Furthermore, the method of ingestion, adverse effects, toxicity, and the drugs' interaction and effectiveness in comparison with other drugs are observed and studied [7, 10] to gather information on the absorption, distribution, metabolism and excretion of the drug [10]. They also examine its potential benefits and mechanisms of action in addition to the best dosage for effective use.

SUBJECT INDEX

A

- Abiotic stresses 2, 52
Acacia 150, 204
 arabica 204
 mearnsii 150
 Acarbose 243, 253
 Accumulating 117, 223, 306
 superoxide anions 306
 Acetylcholinesterase 219, 234
 Acid(s) 3, 4, 5, 9, 23, 24, 51, 52, 71, 97, 100,
 101, 102, 117, 147, 148, 162, 166, 168,
 169, 186, 187, 188, 189, 203, 218, 219,
 225, 229, 243, 245, 246, 249, 250, 255,
 257, 273, 280, 298, 302, 308, 333, 366,
 386
 acetic 386
 arachidonic 71, 219
 aristolochic 333
 aromatic 249
 benzoic 4
 caffeic 97
 carboxylic 245, 246, 249, 250, 255, 280
 cinnamic 100
 coumaric 189
 deoxyribonucleic 273, 298
 deoxyuridylic 117
 eicosapentaenoic 218
 gallic 168, 189, 225
 ellagic 148, 189, 225
 folic 243
 gallotanic 225
 hexahydroxydiphenic 168
 hydroxycinnamic 100, 169
 hydroxyimberbic 166
 mevalonic 51, 188
 nucleic 23, 52, 101, 162, 308
 organic 51, 147
 phenolic 3, 4, 97, 100, 148, 168, 189
 protocatechuic 4, 9
 pseudolaric 102
 salicylic 24, 186
 sargaquinoic 229
 shikimic 51, 187
 synaptic 4
 tannic 168
 thymidylic 117
 tricarboxylic 302
 uric 366
 ursolic 203
Acinetobacter baumannii 151, 191, 193
 Acquired immune deficiency syndrome 40
 Actinic keratosis 114, 126
 Actinomycetes 139, 141, 148
 Action 8, 94, 165, 166, 171, 191, 203, 288
 analgesic 191
 anti-microbial 165
 antioxidant 8
 effective anticancer 288
 inhibitory 166
 insulin 203
 neuroprotective 8
 of secondary metabolites 171
 produced leukopenic 94
 Activation 70, 88, 89, 97, 103, 114, 116, 118,
 123, 124, 147, 273
 signaling pathway 273
 suppressing 124
 Activity 12, 56, 57, 62, 64, 65, 66, 67, 68, 72,
 73, 84, 89, 95, 98, 99, 118, 123, 124,
 140, 147, 152, 165, 169, 189, 191, 192,
 193, 196, 202, 203, 220, 221, 273, 329,
 368, 377, 385
 anti-Alzheimer's 169
 anti-bacteria 192, 193
 anti-bacterial 193
 anti-biofilm 152
 anti-fungal 191
 antihemorrhagic 169
 antineoplastic 95
 anti-oxidant 89
 anti-paralytic 191
 antiproliferative 273
 anti-proliferative 124

Subject Index

anti-thrombotic 123
antitumor 84, 189
anti-viral 196
autophagy-modulatory 221
bacteriostatic 193
enzymatic 124, 377
immunomodulatory 140
malaria-related 385
metabolic 147
photo-protective 118
photosynthetic 220
therapeutic 12, 368, 377
wound-healing 329
Adenosine diphosphate-ribose 383
Adenylosuccinate synthetase 386
Adipogenesis 12
Advanced oxidation protein products (AOPP)
312
Aegle marmelos 245, 251
African traditional medicine 39
Agents 6, 7, 24, 50, 51, 69, 99, 117, 118, 124,
148, 162, 186, 192, 234, 238, 240, 242,
243, 251, 289, 297, 298, 300, 301, 302,
306, 311, 312, 331, 366, 368
allelopathic 51
anti-aging 6
anti-bacterial 192
anti-diabetic 6
antihyperglycaemic 240
anti-inflammatory 69, 99
anti-invasive 124
antineoplastic 300
bacteriostatic 302
biocompatible stabilizing 251
biomedical 148
chemical 117
diabetogenic 243
disease-causing 312
essential neurodegenerative 234
herbal 331
infectious 302
medicinal 7, 186
microbial 162
mitigating 306
oral hypoglycaemic 242

Therapeutic Use of Plant Secondary Metabolites 403

photosensitive 118
prophylactic 148
proteolytic 24
stabilizing 238
toxic 331
Aging world population 229
Aglaia foveolata 197
Agrochemicals 141, 162
Akt pathway 123
Alanine amino-transferase 9
Alcohol dehydrogenase 170, 301
Aldose reductase 382
Alga 152, 164
green 164
Algae 121, 126, 175, 240, 269, 274, 277, 288
brown 121, 126
green 175
red 288
Aliphatic hydrocarbons 308
Alkaloids 1, 7, 8, 30, 32, 51, 91, 93, 94, 95,
100, 149, 161, 162, 169, 170, 190, 191,
199, 201, 205, 245, 247, 255, 278
aromatic 51
monoterpene indole 91
novel bioactive 149
vinca 30, 32, 91, 94, 95, 201
water-soluble 93
Allelopathy 2
Allogenic grafting 375
Aloe vera 244, 245, 251, 346
Alpha amylase activity 7
Alpha-glucosidase 244, 252, 253, 380
Alzheimer's disease 6, 8, 214, 222, 223, 229,
230, 325, 333, 389
Aminoglycosides 143, 298, 300, 304
phosphotransferases 143
Amoxicillin 307
Amphipathic property 141
Ampicillin 59, 60, 62, 64, 143, 144, 300, 301,
303, 309
resistance 144
AMPK activity 205
Amylase 204, 252, 381
enzymes 381
inhibitory activities 252

- Amylose 247
- Anacardium occidentale* 284
- Analysis 26, 97, 186, 250, 326, 329, 331, 332, 333, 334, 347, 349, 353, 354, 355
 - bioactivity identification 349
 - chemical 186
 - chromatographic 26
 - dispersive 250
 - diverse statistical 334
 - energy dispersion 250
 - flow cytometric 97
 - genome-based 353
 - lipid profiling 333
 - metabolic 332, 355
 - microarray 329, 353
 - multi-omics data 331
 - omics-based 326
 - plant system 347
 - regulatory pathway 353
 - regulatory sequences 353, 354
 - spectrometry 354
 - two-dimensional electrophoresis 354
- Ananas comosus* 253
- Andrographis 202, 245, 251, 254, 353
 - aniculata 353
 - paniculata 202, 245, 251, 254
- Angiogenesis 6, 87, 98, 99, 103, 120, 123, 124, 125, 273, 283, 287, 382
 - chorioallantoic membrane 103
 - inhibiting 120, 123
 - inhibits 125
- Anisodamine anisodus 24
- Anisodine anisodus 24
- Anthocyanins 8, 9, 99, 167, 218, 223, 224, 225, 226, 250
- Anti-angiogenesis 101, 103
- Anti-bacteria Activity 193, 194
- Antibacterial 7, 57, 64, 142, 146, 151, 152, 162, 163, 164, 165, 168, 170, 171, 189, 191, 192, 239, 298, 299, 301, 303, 305, 306, 308, 378
 - activities 7, 57, 142, 162, 163, 164, 165, 168, 170, 171
 - agents 192, 239, 298, 299, 303, 306, 308, 378
 - chemotherapy 305
 - drugs 191
 - effect 64
 - gents 306
 - peptides 146, 152
 - stressor 306
- Antibiotic(s) 55, 139, 140, 141, 143, 144, 145, 146, 297, 298, 299, 300, 307, 308, 309, 312, 366
 - aminoglycoside 300
 - bacteriostatic 297
 - carbapenem 143
 - efficacy 146, 312
 - methicillin 144
 - susceptibility 309
- Anti-cancer 30, 85, 90, 91, 101, 103, 122, 273
 - effects 85, 101, 273
 - properties 30, 90, 91, 103, 122
- Anti-cancer agents 84, 90, 91, 118, 121
 - plant-derived 91
- Anticancer chemotherapeutic agents 115
- Anti-cancer compounds 30, 91, 100
 - plant-derived 30
- Anti-carcinogenic activity 6
- Antidepressant activities 10
- Antidiabetic 1, 7, 8, 9, 10, 11, 12, 185, 238, 239, 243, 251, 252, 253, 254, 257, 258, 259, 260
 - action 243
 - activity 9, 11, 185, 251, 252, 253, 257, 260
 - applications 258
 - drugs 243
 - effect 252
 - phytonanoparticles 260
 - therapy 260
- Antifungal 64, 65, 69, 148, 149
 - activities 64, 65, 148, 149
 - effect 65, 69
- Anti-gastric cancer activity 384
- Anti-inflammatory 8, 69, 70, 126, 189, 217, 223, 224, 229
 - activity 8, 69, 126, 217
 - compounds 229
 - drugs 69
 - effects 70, 189, 223, 224

Subject Index

Anti-malarial activities 199
Antimalarial 7, 10, 31, 186, 197, 198, 371, 385, 386
 activity 7, 198, 385, 386
 agents 31
 drugs 10, 31, 186, 197, 371
Antimicrobials 1, 7, 50, 51, 55, 143, 144, 145, 146, 147, 152, 271, 272, 297, 298, 299, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313
 chemotherapy 299
 drugs, conventional 146
 effects 1, 7
 induced cell apoptosis 297
 lethality-oxidative stress link 301
 peptides 145, 147, 152, 303
 photodynamic inactivation (APDI) 311
 resistance 55, 298, 305
 therapy 297, 299, 302, 304, 306, 307, 308, 309, 311
 tolerance 298
 traditional 303
 stressors 307
Antimicrobial action 8, 12, 55, 56, 64, 69, 300, 303, 305, 307
 activities 8, 12, 55, 56, 57, 64, 69, 305
Anti-microbial activities 171
 broad-spectrum 171
 of secondary plant metabolites 171
Antimicrobial agents 2, 147, 167, 298, 299, 305, 306, 308, 310, 313, 385
 bacteriostatic 305
 synthetic 147
Antimigratory effect 126
Anti-obesity activity 12
Antioxidant(s) 6, 50, 51, 52, 71, 72, 73, 122, 123, 125, 126, 146, 147, 166, 167, 215, 218, 219, 220, 221, 222, 224, 234, 239, 271, 298
 activity 6, 72, 126, 222, 234
 agents 271
 defense system 52
 deficiency 298
 enzymes 215, 219, 220
 functions 147

Therapeutic Use of Plant Secondary Metabolites 405

 homeostasis 234
 intrinsic 52
 lipophilic 218
 properties 221
Anti-plasmodic activity 199, 200
Anti-proliferative effects 89, 118, 273
Anti-skin cancer property 122
Antitumor agent 25
Antiulcer drug cimetidine 368
Antiviral 8, 10, 31, 51, 194, 196, 197
 activities 8, 10, 51, 194, 196, 197
 agents 10, 31
Antiviral effects 32, 195
 synergistic 32
Apoptosis 10, 85, 88, 93, 97, 100, 103, 115, 120, 124, 125, 126, 202, 203, 273, 283, 284, 285, 286, 287, 288, 330
 acid-induced 97
 hypoglaucum-induced 330
 induced 97, 124, 284, 285, 287
 induction 10, 103, 120, 288
 pathways 203
Apoptosome 88
Apoptotic 88, 330
 effects 330
 signalling 88
Applications 50, 74, 75, 146, 117, 238, 239, 240, 259, 260, 269, 270, 272, 274, 279, 311, 325, 343, 347, 357, 376, 380
 agricultural 146, 274
 bioinformatics-assisted computational 347
 biomedical 270, 272, 279, 376
 photodynamic therapy 117
 therapeutic 50
Argyrea nervosa 245
Aromatherapy 51
Aromatic bioactive 150
Artemisinin 24, 31, 32, 33, 102, 189, 197, 303, 371
 popular antimalarial drug 33
Arthritis 69, 223, 304
 rheumatoid 69
Artificial lipid membranes 174
Aspergillus 67, 68, 148, 152, 276
 brasiliensis 68

- flavipes* 152
 - fumigates* 276
 - fumigatus* 148
 - niger* 67
 - oryzae* 152
 - Assays 72, 73, 243, 256, 372, 373
 - phenotypic 372
 - phospholipid peroxidation 72
 - Asthma 8, 52, 69, 325, 378
 - Atheromatous lesion 9
 - Atherosclerosis 69, 70, 226, 304
 - Atomic condensation 240
 - ATP hydrolysis 174
 - Azadirachta indica* 196, 199, 245, 251, 385
- B**
- Bacillus* 12, 57, 58, 59, 60, 62, 63, 169, 276, 305
 - anthracis* 169
 - cereus* 12, 57, 58, 63, 276
 - flexus* 276
 - megaterium* 276
 - subtilis* 12, 57, 58, 59, 60, 62, 63, 305
 - Bacteria, thermophilic 276
 - Bacterial 165, 298, 299, 301, 313
 - adaptation mechanisms 313
 - cell death 301
 - diseases, infectious 165
 - prostatitis 299
 - responses 298
 - Bactericidal 141, 169, 173, 297, 298, 301, 302, 304, 305, 306, 312, 313
 - agents 297, 298, 302, 305, 312, 313
 - antibiotics 298, 301, 304, 313
 - antimicrobial agents 306
 - effect 141
 - Bacteriocins 140, 147, 152, 153
 - Bacteriophages 55
 - Basal cell carcinomas (BCCs) 112, 113, 114, 119
 - syndrome 119
 - Basal keratinocytes 113
 - Bax 101, 288
 - apoptotic proteins 288
 - pathways 101
 - Berberis vulgaris* 170, 171, 194
 - Biflavonoid 123
 - Binding 381, 384, 385, 386, 389
 - affinity 381, 385, 386, 389
 - docking-derived 385
 - energy 384
 - Bioactive 97, 125, 126, 145, 146, 147, 152
 - peptides 145, 146, 147, 152
 - phytochemical 125, 126
 - plant compound 97
 - Bioactive compounds 122, 149
 - plant-based 149
 - plant-derived 122
 - Bioactive flavonoid 98, 123
 - compounds 123
 - in cancer treatment 98
 - Bioactivities 22, 50, 97, 122, 146, 148, 335, 344, 354, 384
 - numerous 122
 - Biobank 326
 - Biocompatibility 239, 271, 288, 291
 - nature 288
 - Biodegradable stabilizing 251
 - Biofilm formation 65, 174
 - inhibited 174
 - Bioinformaticians 325
 - Bioinformatics 21, 34, 35, 121, 326, 343, 345, 346, 347, 348, 349, 354, 357, 365, 366, 375, 389
 - analyses 326, 345
 - programs 343
 - techniques 375
 - tools 121, 343, 348, 349, 354, 357
 - Biologic license applications (BLAs) 372
 - Biomarkers 121, 271, 229, 312, 313, 325, 327, 344, 345, 357
 - imaging 229
 - targeted disease 345
 - Biomedical 276
 - industry 276
 - Biomedicine industry 344
 - Biomolecular immobilization 271

Subject Index

Biosynthesis 3, 8, 51, 52, 173, 174, 351, 353, 377
 fatty acid 173
 pathway 51, 353
 peptidoglycan 173
Biotic antagonists 2
Blood transfusion 194
Body secretion 324
Botanogenomics 328
Bovine serum albumine (BSA) 279
Brain 10, 218, 219, 222, 224, 229, 230, 231, 233, 379, 383
 cancer 379, 383
 concentration 219
 diseased 230
 function 224
 type creatine kinase 383
Brassinosteroids 52
Breast cancer 31, 95, 202, 227, 271, 330, 382, 383, 384, 388
Butyrylcholinesterase 234

C

Calophyllum 31, 245
 lanigerum 31
 tomentosum 245
Camellia sinensis 99, 126, 202
Camptotheca acuminata 91
Camptothecin 91, 92
Camptothecin derivatives 91
Campylobacter jejuni 57, 58, 59, 60, 62, 63, 64
Cancer 10, 30, 31, 32, 84, 85, 86, 89, 94, 97, 100, 118, 127, 200, 202, 227, 271, 272, 282, 286, 325, 326, 371, 379, 383
 colon 97, 202
 endometrial 202
 gastric 94
 mucosal 127
 ovarian 202, 271, 286
 plasma cell 272
 prostate 10, 325, 379
 target proteins 383

Therapeutic Use of Plant Secondary Metabolites 407

 therapy, targeted molecular skin 118
 vaccinations 200
Cancer cell(s) 85, 86, 88, 98, 99, 103, 114, 115, 116, 255, 256, 271, 272, 273, 284, 285, 287, 382
 gastric 287
 human liver 256
 imaging 272
 migration 98, 103, 382
 motility 98
 proliferation 382
Candida 8, 12, 65, 66, 67, 68, 69, 149, 170, 385
 albicans 8, 12, 65, 66, 67, 68, 69, 149, 170
 parapsilosis 12
 pseudotropicalis 12
 stellatoidea 12
 sativa 385
Capability 87, 93, 169, 240, 224, 271, 304
 absorptive 240
 developthe 87
Capacity 32, 52, 101, 120, 217, 234, 273, 370, 386
 antioxidant defense 52
 host defense 32
 nanoparticle-mediated anti-proliferative 273
 therapeutic 101
Capparis spinosa 172
Carbapenemase 303
Carcinogenesis 9, 87, 88, 89, 121, 122, 124
 bioactive compounds halt skin 122
 induced lung 9
 induced skin 124
Carcinogenicity 385
Carcinoma 87, 95, 101
 testicular 95
 thyroid 101
Carotenoids 118, 121, 147, 204, 216, 220, 221, 223, 226, 227, 234
Carrageenan-induced peritonitis 70
Cassia 199, 246
 fistula 246
 siamea 199
Catharanthus roseus 30, 94, 95, 201, 371

- Cell 73, 86, 88, 89, 95, 96, 98, 100, 118, 123, 202, 272, 273, 287
apoptosis 96
cycle 86, 98, 273
cytotoxicity 73
homeostasis 89
proliferation 88, 95, 100, 118, 123, 202, 272
viability, cancerous 287
- Cell cycle arrest 9, 101, 103, 120, 121, 125, 126, 201, 202, 284, 287
and apoptosis 202
- Cell death 88, 89, 161, 169, 170, 173, 287, 288, 297, 298, 305, 306, 312, 313, 382
microbial 298, 305
programmed 382
stress-induced 312
- Cell growth 123, 141, 253, 287, 330
arrest 330
- Cellular 117, 284
carcinoma 284
metabolic machinery 117
- Central nervous system (CNS) 218, 233
- Cephalotaxus* 95, 96
hainanensis 96
harringtonii 95
- Chaetomium globosum* 152
- Chain 224, 273, 298, 302
electron transport 273, 302
nucleotide 298
- Challenges 37, 38, 41, 123, 216, 232, 365, 369, 371, 374, 378, 380, 387
economic 380
environmental 216
- Chemicals 27, 29, 216, 225, 227, 228, 234, 241, 328, 331, 375, 383
neuroprotective 234
respiratory 216
- Chemical structure 4, 189, 227
of phenolic acids 4
of Plant sterols 227
of classes of terpenoid 189
- Chemoprevention 124
- Chemotherapeutic agents 114, 117, 118, 300, 302
bacteriostatic 302
- Chemotherapeutic drugs 84
- Chemotherapy 31, 40, 87, 114, 115, 117, 119, 122, 124, 200, 270, 289
conventional 289
resistance 117
- Chlamydia trachomatis* 299
- Chlamydomonas reinhardtii* 164
- Chlorella vulgaris* 277
- Cholesterol drugs 12
- Cholinergic synapses 234
- Cholinesterase 234
- Chromatin immunoprecipitation 353
- Chronic 95, 223, 272, 379
lymphocytic leukemia (CLL) 272, 379
myeloid leukaemia 95
sicknesses 223
- Cigarette smoke (CS) 71
- Cinchona officinalis* 186
- Ciprofloxacin 301, 306
- Cleome viscosa* 283, 286
- Clinacanthus nutans* 284
- Cnidium monnieri* 172
- CNS 217, 218
degeneration 217
related diseases 218
- Cocaine 8, 186, 190
- Colitis 69, 70, 71
- Colonocytes 71
- Colorectal cancer 85, 202, 203, 222, 379
- Column chromatography (CC) 29
- Combination therapy 146, 297, 305, 313
- Combinatory effects 375
- Comparison of molecular field analysis (CoMFA) 385
- Computational 35, 36, 343, 347, 348, 353, 354, 365, 369, 375, 376, 377
algorithms 375
associated drug design (CADD) 369, 376, 377
genomics analysis 348
metabolomics analysis 354
proteomics analysis 354
software 36
techniques 35
tools 343, 347, 354, 365

Subject Index

transcriptomics analysis 353
Computer-aided drug discovery 376
Concentration 11, 65, 141, 173, 174, 218, 219, 283, 284, 285, 286, 287
 plasma insulin 11
 reducing plasma glucose 11
Conditions 38, 215, 217, 234
 environmental 38
 neurodegenerative 215, 234
 neurotoxic 217
Conjunctiva 113
Constipation 6, 289
Contamination, bacterial 141, 150
Conventional 55, 114, 185, 369
 medicines 55, 185
 methods of drug development 369
 mucocutaneous cancer therapy 114
Coronavirus 21, 194, 195, 325
 infection disease 21
Correlation, metabolic 355
Cosmetics 50, 51, 52, 53, 141, 150, 151, 162, 215, 239
 additives 53
 industries 150
Cosmetology 269
Costus pictus 246
Coupling microarray gene expression analysis 329
Couroupita guianensis 246, 254
COVID-19 21, 32, 33
 outbreak 32
 pandemic 33
 responses 33
CRISPR technology 375
Crohn's disease 378
Curcuma longa 122, 202, 283, 287
Cyanobacteria 269, 274, 277
Cyanobacterium 175
 photosynthesizing 175
Cyanotherapeutics 40
Cyclin-dependent kinases (CDKs) 100, 383
Cyclooxygenase 97, 200
Cyclophosphamide 114, 286
 cytotoxic effects 286
Cysteine protease 199

Therapeutic Use of Plant Secondary Metabolites 409

Cytokines 8, 200, 273, 330
 inflammatory 273
Cytotoxic activity 74, 191, 277, 288
Cytotoxicity 50, 73, 75, 100, 118, 124, 197, 256, 272, 273, 284, 286, 324
 effects 324
 properties 50, 75

D

Damage 8, 52, 87, 117, 119, 122, 215, 219, 222, 233, 242, 300, 302, 311
 neuronal 219
 cancer cells 87
 plant cells 52
Databases 36, 40, 141, 185, 329, 343, 345, 347, 348, 349, 350, 356, 357
 genome sequence 348
 natural product 40
Data 36, 354
 mining 354
 processing 36
Deaths 32, 33, 84, 85, 143, 144, 147, 150, 231, 232, 282, 286, 298
 cancer-causing 85
Defect 203
 progressive insulin secretory 203
Defective apoptosis mechanisms 115
Defences 149, 298, 309, 310
 bacterial 309
 innate chemical 149
Dehydrogenase 199, 273
 lactate 273
Delayed-type hypersensitivity 69
Dementia 8, 214, 215, 216, 218, 223, 228, 229
 vascular 214
Dendrilla 150
 antarctica 150
 membranosa 150
Dengue fever 196
 type-2 virus replication 196
Density functional theory (DFT) 384, 386
Deoxynucleotide synthesis 379
Depletion 234

- cholinergic 234
- Depression 8, 11, 223
- Destruction 89, 114, 116, 256, 302
 - observed morphological 256
 - oxidative 302
- Detection 163, 272, 328, 373
 - fluorescence 328
- Detrimental effect 161
- Development 22, 33, 37, 38, 39, 41, 85, 217, 298, 307, 326, 332, 365, 366, 367, 368, 369, 370, 371, 372, 377, 378, 388
 - fast technology 326
 - herbal 33
 - socioeconomic 85
 - technological 370
 - urban 85
- Devices 36, 239
 - liquid handling 36
 - photocatalytic 239
- Dextran sulfate sodium (DSS) 71
- Diabetes 6, 11, 21, 22, 69, 203, 204, 205, 238, 241, 243, 244, 258, 365, 377, 380, 381
 - gestational 203
 - mellitus 69, 203, 204, 205, 241, 258, 381
 - treatment 381
- Diabetic therapy 260
- Diarrhea 6, 243, 270
- Dietary 221, 222
 - efficacy 221
 - minerals 222
- Disc diffusion 57, 58, 59, 60, 61, 62, 63, 65, 66, 67, 68
- Discovery, ethnobotanical 22
- Disease(s) 21, 23, 32, 39, 86, 121, 185, 197, 200, 203, 214, 215, 222, 223, 229, 230, 299, 324, 325, 326, 328, 333, 344, 345, 346, 353, 371, 378, 379
 - autoimmune 203
 - cardiovascular 39, 325, 344
 - cerebrovascular 353
 - communicable 21
 - drug-resistant 185
 - endemic 197
 - immunoinflammatory 328
 - inflammatory 325
 - life-threatening 333
 - neglected tropical 39
 - neurological 223
 - non-neurodegenerative 229
 - sickle cell 344
 - stratification 121
 - transmitted 299
 - urinary stone 325
 - urologic 325
- Disease process 229, 366
 - neurodegenerative 229
- Disease therapy 304, 308, 312
 - cardiovascular 304
- Disorders 22, 113, 214, 370, 378
 - depressive 22
 - genetic 113
 - inflammatory 378
- DLS spectroscopy 281
- DNA 40, 50, 89, 99, 117, 169, 170, 171, 172, 193, 194, 273, 282, 286, 298, 328, 299, 300, 301, 326, 327, 328, 348, 366, 379, 380
 - alkylating agent 379
 - and intracellular nitrogenous base proteins 286
 - and protein synthesis inhibition 193
 - barcoding method 328
 - based techniques 328
 - breakage, cellular 99
 - chips 328
 - degeneration 282
 - protection 50
 - recombinant technology 366
 - repair enzymes 89
 - replication 117, 273
 - sequencing 40, 348
 - synthesis 171, 194
- DNA damage 51, 87, 114, 273, 288, 301, 309
 - and accumulation of genetic events 87
 - and apoptosis 288
 - protection 51
- Docking 382, 383, 385, 386, 387
 - analysis 382, 383, 385
 - methods 386
 - process 387

Subject Index

Downregulation 9, 123, 202
Downstream 277, 291, 329
 effects 329
 processing 277, 291
 signalling, suppressing 98
Drug(s) 21, 22, 24, 25, 26, 30, 35, 37, 85, 91,
 104, 145, 175, 186, 191, 194, 197, 242,
 270, 278, 328, 332, 366, 367, 371, 377,
 378, 387
 anti-malaria 197
 anti-microbial 175
 antitumor 377
 antiviral 194, 366
 conventional 104, 242, 371, 387
 metabolism 328, 377
 production 278
 synthesis 26
Drug delivery 270, 291
 systems 291
 therapeutic 270
Drug design 36, 366, 368, 369, 370, 384, 387,
 389
 computer-assisted 370
 computer-assisted rational 369
Drug development 21, 26, 27, 36, 37, 38, 41,
 323, 365, 368, 369, 370, 371
 process 26, 27, 37, 41, 323
Drug discovery 36, 365, 372
 green 36
 target-based 372
 traditional 365
Drug discovery 37, 373, 390
 computational applications 390
 efforts 37, 373
Drug discovery process 21, 26, 27, 35, 37, 40,
 372, 380, 387
 target-based 37
Drug resistance 55, 139, 143, 144, 145, 146,
 303
 genes 143
 mechanisms 146
 therapy 303
Dynamic light scattering (DLS) 240, 246, 247,
 248, 249, 281
Dysentery DNA gyrase 380

Therapeutic Use of Plant Secondary Metabolites 411

Dysfunction 6, 215, 231
 mitochondrial 215
 neuronal 231
 renal 6
Dyslipidemia 226

E

Ebola 21, 197, 377
 and coronavirus infection disease 21
 virus 197, 377
Edema 71, 289
Edible vaccine 23
Effectiveness 33, 115, 118, 139, 140, 150,
 152, 175, 186, 241, 285, 332, 371
 anti-biofilm 152
 broad-spectrum antimicrobial 152
 therapeutic 371
Effector-triggered immunity (ETI) 174
Efficacious antimalarial drug 31
Efficacy 28, 29, 30, 32, 37, 38, 41, 123, 146,
 149, 151, 168, 297, 299, 307, 308, 309
 anti-microbial 168
 tumor 123
Efficiency of Bioactive Compounds 147
Efflux pump (EP) 172, 173, 174, 193, 310,
 311
 bacterial 310
 inhibitor(s) (EPIs) 172, 173, 174, 193
Efforts, holistic 41
EGFR kinase 383
Electrodesiccation 115
Electrolysis 274
Electrophoresis 328, 354
 microchip 328
Elephantina elephantorrhiza 244
Emerging infectious diseases 32
Endocrinopathies 203
Endophytic 139, 141, 152
 bacteria 139
 fungi 139, 141, 152
Endosymbiosis 163, 164, 175
 relationship 175
Energy 174, 239, 240, 250, 281, 333

- consumption 240
 - dispersive X-ray spectroscopy 281
 - reservoir 333
 - storage 239
 - Enterobacter* 57, 148
 - aerogenes* 57
 - cloacae* 148
 - Enterococcus* 58, 59, 60, 61, 148, 168, 191, 194
 - faecalis* 58, 59, 60, 61, 148, 168
 - faecium* 191, 194
 - Environment 23, 51, 52, 141, 191, 216, 250, 258, 304, 310, 311, 327
 - marine 141
 - Environmental stresses 2, 328
 - Enzyme(s) 8, 11, 89, 91, 92, 200, 216, 217, 218, 240, 244, 269, 274, 277, 278, 305, 310, 384
 - aromatase 384
 - cyclooxygenase 217
 - DNA topoisomerase 91
 - lipoxygenase 218
 - oxidase 310
 - pancreatic 244
 - sensitive 244
 - topoisomerase 200
 - Enzymatic hydrolysis 5
 - Enzymatic systems 117, 171
 - thiol-dependent 171
 - Epicatechin gallate 9
 - Epidermal growth factor receptor (EGFR) 98, 120, 379, 383
 - Epidermal keratinocytes 114
 - Episodic memory activity 220
 - Epithelialmesenchymal transition 126
 - Eridictyon californicum* 194
 - Eriodictyon californicum* 172
 - Ervatamia chinensis* 149
 - Erythromycin 62, 68
 - Escherichia coli* 57, 58, 59, 60, 61, 62, 63, 64, 148, 151, 152, 298, 301
 - Essential 55, 228
 - glucosinolate sources 228
 - oils major compounds 55
 - Ethnobotany 30
 - Ethnomedicine 30
 - Ethosomes 125
 - Eucalyptus tree 152
 - Euphorbia thymifolia* 381
 - European medicines agency (EMA) 290
 - Expressed sequence tags (ESTs) 348
 - Expression 9, 69, 70, 71, 124, 150, 204, 216, 222, 309, 310, 331, 353
 - inflammatory cytokines 69
 - regulating adaptive genes 309
- F**
- Factors 100, 102, 219, 229, 271, 272, 273, 357, 383
 - angiogenic 100
 - disease-promoting 229
 - heparin-based growth 272
 - neurotrophic 219
 - transcription 102
 - transcriptional 100, 357
 - vascular endothelial growth 100, 271, 273, 383
 - Failure 26, 27, 69, 203, 388
 - congestive heart 69
 - Fatigue 254, 270, 289
 - Fatty acids 1, 7, 12, 139, 141, 216, 218, 223, 227
 - essential 216, 223
 - Fenton 298, 306
 - pathway 298
 - reaction 306
 - Ferritin-like protein (FLP) 279
 - Fetal intestine 373
 - Fever, typhoid 161, 170
 - Fibrosis 353
 - cystic 203
 - Ficus* 199, 247, 284
 - fistulosa* 199
 - glomerata* 247
 - krishnae* 284
 - Flavoenzymes 306
 - Flavonoids 124, 167
 - glycosylated 124

Subject Index

hydrophilic 167
natural dietary 124
Flux analysis 355
metabolic 355
Flux analyzer 355
metabolic 355
Folic acid synthesis enzyme 380
Food(s) 52, 53, 55, 100, 139, 140, 141, 146,
148, 150, 151, 162, 201, 215, 216, 220,
221, 222, 223, 224, 226, 227, 242, 290
and drug administration (FDA) 201, 290
flavoring 52
industries 52, 53, 150, 162
information systems 141
organic 227
plant-based 139, 140
plant-derived 100
poisoning 55
production processing 151
proteinous 242
sources of vitamin 222
Fortifications 304, 312
block antioxidant 304
Fourier transform infrared spectroscopy 280,
281
Fractionation 29, 91, 116
chromatography-guided 29
Free energy 387
Free radicals 71, 89, 169, 218, 222, 224, 225,
241, 300, 310
and anti-oxidants in relation 89
reactive 89
Fruits 6, 98, 120, 124, 126, 168, 188, 218,
220, 222, 223, 224, 245, 250, 277
citrus 188
edible 168
FT-IR spectroscopy 280
Functional 112, 115, 147
foods 147
impairment 115
transitions 112
Functions 3, 6, 22, 38, 117, 161, 169, 171,
173, 217, 219, 221, 222, 223, 225, 272,
298, 299, 324, 325, 334, 372
anti-cancer 225

Therapeutic Use of Plant Secondary Metabolites 413

chloroplast 3
isothiocyanates 219
mental 217
protective 221
resveratrol 6
therapeutic 22, 38
Fungal growth 66, 67
Funtumia elastica 172
Fusarium 66, 68, 276
cerealis 66, 68
semitectum 276
Fusobacterium nucleatum 62, 64

G

Gallocatechins 5
Gallotannins 168
Gardnerella vaginalis 57, 58, 64, 65
Gas chromatographic-mass spectrometry 334
Gastrointestinal erosion 69
Gazania krebsiana 244
GC-MS techniques 333
GenBank 356
Genes 36, 37, 52, 86, 87, 111, 114, 174, 200,
273, 282, 286, 306, 325, 327, 328, 329,
330, 348, 351, 353, 354, 374, 375, 378
anti-apoptotic 282, 286
apoptotic 273
combinations influence 375
defense 52
editing 374
editing technologies 374
efflux pump 174
enzyme 306
metabolic 351
nucleotide excision repair 114
ontology 354
targeting multiple carcinogenetic 111
tumor suppressor 200
tumour suppressor 273
Gene expression 89, 100, 202, 311, 327, 328,
330, 349, 356
mechanisms 330
omnibus (GEO) 349, 356

processes 330
Genetic 113, 114, 328
 dysregulation 113
 syndromes 114
 toxicants 328
Genitourinary tract 113
Genomes 164, 194, 327, 344, 347, 348, 351,
 353, 354, 374
 nuclear 164
 viral 194
Genomic 325, 326
 information 325
 revolution 326
Genomics 34, 35, 323, 325, 326, 328, 343,
 344, 345, 346, 347, 349, 350, 351, 352
Geographic information system (GIS) 34
Ginsenosides 205
GIT disturbances 243
Global health challenges 21
Gluconeogenesis 244
Glucose 6, 9, 11, 203, 228, 241, 244, 382
 absorption 9
 digestion 382
 homeostasis 6
 intolerance 203
 utilization 11
Glucosidase 204, 252, 381
 activities 204
Glutaminylcyclase 216
Glutathione 100, 163, 215, 312
G peroxidases 100, 215
Glycogenesis 204
Glycolysis 11, 204, 244
Glycoproteomics 323, 330
Glycosides 4, 51, 187, 196, 204, 245, 247,
 248, 249, 346
Glycyrrhiza glabra 151, 385
Gossypium arboreum 199
Gracilaria verrucosa 285
Grape 126, 240, 291
 seeds proanthocyanidins (GSPs) 126
 nanoparticle synthesis 291
 nanotechnology 240
Green synthesis 240, 257, 259, 270, 272, 274,
 276, 277, 278, 290

 of nanoparticles 240, 259, 269, 278
Growth 52, 101, 118
 factor receptor 118
 promoting activity 52
 tumor 101
Gut 147, 332
 microbiomes 332
 microbiota 147

H

Haber-Weiss reactions 302
Haemoglobin level 243
Haemophilus influenzae 144
Hair follicles 113
Hallmark pathologies 229
Halymenia poryphyroides 247
Headache 52, 243
 stress-induced 52
Head and neck cancer 379
Health threats 234
Heart disease 9, 223
 coronary 9
Hedgehog pathway 119
Helicobacter pylori 144, 168
Hemolytic activity 11
Hemorrhagic stroke 233
Hemozoin polymerization 199
Hepatitis 194, 195, 197, 299
 virus 194, 195
Hepatocytes 254
Hepatoprotective 8, 189
 activity 8
Herbal 25, 33, 38, 39, 164, 185, 186, 324, 334
 drug formulation 186
 medicines 25, 33, 38, 39, 164, 324
 plants 185, 186
 preparations 334
Heterocyclic 164, 169, 255
 nitrogen compounds 169
 protists 164
High-content screening (HCS) 373
High-performance 29, 370, 375

Subject Index

liquid chromatography (HPLCs) 29, 370, 375
thin layer chromatography (HPTLC) 29
High resolution transmission electron microscopy 250
High throughput screening (HTS) 28, 34, 35, 36, 369, 376
HIV therapy 31
Holarrhena 172, 193
 antidysenterica 172
 floribunda 172, 193
Homeostasis 52, 147, 273, 298, 305
 disorder 273
Homoharringtonine 95, 96, 201
Human 39, 40, 163, 194, 195, 196, 254, 284, 299, 373, 381
 African Trypanosomiasis 40
 ailments, degenerative 381
 colon adenocarcinoma 254
 gastric adenocarcinoma 284
 immunodeficiency virus (HIV) 39, 194, 195, 196, 299
 intestinal organoids 373
 lung adenocarcinoma 254
 papillomavirus 195
 pathogens 163
Huntington's disease 215, 222, 231, 232
Hydrocortisone 71
Hydrogen 89, 167, 298, 305, 306
 bonding 167
 peroxide 89, 298, 305, 306
Hydrophobic 11, 123, 167
 aglycone 11
Hyperglycaemia 241
Hyperlipidemia 203
Hyperpyrexia 325
Hypertension 244, 325, 371
Hypodermic syringes 194
Hypoglycemia 204
Hypoglycemic activities 11

I

Illnesses 85, 144, 215, 230, 233

Therapeutic Use of Plant Secondary Metabolites 415

cancer-related 144
 multifactorial 230
 neurodegenerative 233
Immune 69, 87, 93, 101, 116, 147, 174, 175, 191, 200, 201, 225, 310, 331
 reactions 225
 response 93, 101, 116, 174, 175, 200, 331
 system 69, 87, 116, 147, 174, 191, 201, 310, 331
Immunity 122, 174, 331
 effector-triggered 174
 microbial-associated molecular-patterns-triggered 174
Immunization, global 23
Immunoassays 29, 312, 372
 ultrasensitive non-radiometric 372
Immunosuppressing effects 69
Immunosuppression 113
Immunotherapeutic tumor arresting activity 383
Immunotherapy drugs 116
Inactivation 168, 169, 196, 202, 311
 antimicrobial photodynamic 311
Induced 283, 285, 329
 cell death 283
 cytotoxicity 285
 transcriptional effects 329
Induction 10, 11, 95, 101, 118, 126, 147, 201, 273, 298, 310
 tumour suppressor proteins 118
Industries 33, 35, 41, 50, 51, 53, 64, 74, 75, 307, 369
 agrochemical 35
 medical 307
 nutraceutical 51
 perfume 53
Infections 2, 6, 8, 22, 31, 32, 40, 55, 140, 143, 144, 145, 150, 167, 233, 235, 305, 307, 308, 310, 311, 312, 328
 dental 6
 invasive 144
 methicillin-resistant *Staphylococcus aureus* 150
 microbially-induced 167
 microflora 328

- neurodegenerative 233, 235
 - parasitic 22, 40
 - pathogenic 2, 8
 - respiratory 312
 - upper respiratory tract 55
 - yeast 55
 - Infectious diseases 21, 139, 140, 145, 146, 148, 153, 161, 170, 175, 194, 333
 - dangerous 333
 - Inflammation 22, 31, 69, 70, 71, 122, 124, 125, 217, 219, 226, 229
 - colonic 70
 - reactions 69
 - Inflammatory 125, 273
 - activity 125
 - response 273
 - Influenza virus 195, 196
 - Information 281, 344
 - phytochemical 344
 - topographical 281
 - Inhibited 65, 71
 - indomethacin-induced gastric lesions 71
 - inflammatory cytokines 71
 - morphogenesis 65
 - planktonic 65
 - Inhibition 6, 7, 8, 9, 11, 12, 50, 69, 71, 123, 166, 171, 172, 173, 193, 197, 199, 204, 253, 298, 301, 305, 384
 - acetylcholinesterase 50
 - gastric cancer 384
 - of cysteine protease 199
 - of DNA and protein 171, 172
 - of DNA gyrase 172, 173, 193, 301
 - of HBV DNA replication 197
 - of amylase and glucosidase activities 204
 - urease 171
 - Inhibitors 95, 116, 119, 139, 146, 171, 173, 229, 235, 243, 377, 382, 384
 - antiviral 377
 - cyclin-dependent kinase 95
 - Inhibitory activities 369, 386
 - Injury 6, 8, 69, 122, 214, 273
 - cytoskeletal 273
 - hematopoietic system 122
 - traumatic brain 214
 - Instability 273, 302
 - chromosome-producing genomic 273
 - iron-sulphur cluster 302
 - Instruments 233, 238, 378, 389
 - microglial initiation 233
 - spectroscopic 238
 - Insulin 11, 203, 204, 241, 242, 243, 256, 258
 - producing 203
 - injections and oral anti-diabetic agents 203
 - potentiation effect 256
 - release 11
 - resistance 203
 - signalling pathways 204
 - stimulating effect 256
 - Insulin secretion 203, 204, 205, 244, 256
 - enhanced pancreatic 256
 - glucose-stimulated 205
 - Integration 185, 329, 331, 343, 344, 347, 353
 - multi-omics data 343, 344
 - Interactions 23, 149, 164, 166, 167, 298, 299, 300, 305, 308, 313, 331, 334, 354, 380, 382, 383, 384, 386, 389,
 - electrostatic 308
 - intermolecular 386
 - ligand-protein 389
 - metabolic 313
 - protein-ligand 380, 384
 - protein-protein 354
 - symbiotic 164
 - tannin-protein 149
- J**
- Junin virus 10
- K**
- Kaposi's sarcoma 112
 - Kidney 234, 333
 - disorders 234
 - problems 333
 - Klebsiella pneumoniae* 12, 58, 59, 60, 61, 149, 172, 191, 193, 276

Subject Index

L

Lactobacillus rhamnosus 152
Laser 274, 282
 ablation 274
 irradiation 282
Legumes 168, 221, 224, 227
 forage 168
Lesions 71, 117, 120
 neoplastic dermatological 120
Lessertia montana 244, 248, 253, 255
Lethality 166, 302, 304, 306
 aminoglycoside 306
 antibacterial-mediated 302
 antibiotic-induced 304
Leucosidea sericea 248, 252
Leukocytospermia 299
Ligningomisin 197
Lipid hydroperoxides 89
Lipidomics Toxicometabolomics 327
Lipid peroxidation 8, 218, 220, 234, 300
Liquid chromatography 29, 331
 high-performance 29
 mass spectrometry 331
Listeria monocytogenes 57, 58, 59, 60, 62, 63,
 64, 148, 166, 171
Liver 9, 11, 85, 218, 222, 234, 244, 325
 aspartate aminotransferase 9
 cancers 85
 disease 325
Lonicera japonica 248
Low-density lipoprotein 227
Lung cancer 96, 202, 227, 271, 282, 283, 284,
 286, 288, 383
 cells 282, 283, 284, 286, 288
 development 227
Lung inflammation 71
Lupinus 149
 albus 149
 angustifolius 149
 luteus 149
Lymphoma 379
Lysosomal protease 379

Therapeutic Use of Plant Secondary Metabolites 417

M

Macromolecule(s) 301, 383
 cancer cell proliferation 383
 oxidation 301
Macrophages 70, 273, 310
Mahonia aquifolium 170
Malaria 10, 21, 31, 33, 39, 161, 197, 205, 371,
 384
 diseases 197
 infections 197
Malignant 113, 124
 melanocytic neoplasm 113
 transition 124
Management 127, 191, 194, 197, 345
 non-toxic 127
 of bacterial infections 191
 of malaria diseases 197
 of viral infections 194
 plant-based diseases 345
MAPK signaling pathways 202
Mass spectrometry 121, 354, 375
Matricaria chamomilla 282
Measure 191, 355
 metabolic flux 355
 therapeutic 191
Mechanisms 9, 10, 100, 101, 102, 103, 111,
 120, 123, 145, 147, 187, 204, 205, 222,
 234, 243, 257, 305, 333, 367
 anti-angiogenesis 100
 anti-cancer 102
 anti-carcinogenic 120
 antimicrobial 305
 anti-tumour 101
 immunomodulatory 111
Medications 6, 30, 234, 382
 anti-inflammatory 234
 efficient chemotherapy 382
Medicinal 50, 194, 347, 357
 herbs 50, 194
 plant research 357
 plant science 347
Medicine 121, 162, 185
 ancient Chinese 162

- contemporary 185
- effective therapeutic 121
- Melanocytes 113
 - dendritic 113
- Melanoma 112, 113, 114, 115, 116, 119, 120, 121, 124, 125, 126, 127
 - cutaneous malignant 114, 119
 - malignant 112
 - skin cancers 112
 - treatment 121, 124
- Melanoma cells 119, 121, 125
 - malignant 125
- Mentagrophytes 65
- Merkel cell carcinoma 112
- Metabolic 52, 141, 162, 164, 185, 258, 298, 299, 313, 333, 343, 344, 345, 347, 351, 353
 - disorder 258
 - pathways 141, 162, 333, 343, 344, 345, 351
 - processes 52, 164, 298, 299, 313, 347, 353
 - syndrome 185, 299
- Metabolism 1, 94, 175, 200, 203, 244, 270, 300, 304, 330, 332, 367, 372, 375, 385
 - chloroplast 175
 - mitochondrial 94
 - regulating cell growth 200
 - respiratory 300
- Metabolites 1, 3, 104, 185, 187, 193, 194, 307, 327, 329, 332, 333, 348, 355, 357
 - endogenous 187
 - natural 104
 - reactive oxygen 307
- Metabolomics 121, 323, 325, 329, 332, 333, 334, 335, 343, 345, 347, 349, 355, 357
 - profiling 334
 - techniques 121
- Metal ions 241, 251, 254, 257, 259, 278, 279, 281
- Metalloproteinases 9, 123, 125
- Metal nanoparticles 269, 270, 275, 276, 277, 278, 279, 280, 281, 285, 291
 - cyanobacteria-mediated 277
 - green synthesis of 275, 277
- Metastasis 6, 99, 100, 101, 103, 114, 120, 123, 124, 125, 271, 272
 - tumor cell 99
- Methicillin-resistant *Staphylococcus aureus* (MRSA) 144, 145, 150, 151, 152, 167, 172
- Methods 57, 117, 163, 312, 368, 380, 371, 388
 - bioluminescent 57
 - chromatographic 312
 - computational chemistry 380
 - computational drug design 368
 - high-performance screening 163
 - machine learning 388
 - nanotechnology 371
 - radiation 117
- Microbes 2, 23, 55, 141, 162, 168, 170, 274, 277, 285, 308, 310, 312
 - commensal 308
 - drug-resistant 55
 - pathogenic 162
- Microbial cells 51, 55, 161, 169, 171, 173, 191, 297, 298, 299, 306, 307, 312, 378, 380, 381
 - diseases 378, 380, 381
 - infections 51, 55, 161, 191
 - reactions 299
 - species, aerobic 298
 - stressed 297
- Microbiota, intestinal 166
- Microenvironment 306, 309, 313
 - oxidatively stressed 306
 - stressed cellular 309
- Microscopic imaging 373
- Microscopy 250, 281, 312, 372
 - atomic force 250, 281
 - electron 372
- Microwave irradiation 274
- Migration 8, 118, 124
 - neutrophil 118
- Minimum inhibitory concentrations (MICs) 56, 64, 68, 146, 170
- Mitigate toxin effects 140
- Mitochondrial 94, 123, 125, 200, 222, 231, 288, 384
 - function 222, 231
 - membrane 94

Subject Index

membrane potential (MMP) 123, 125, 200, 288, 384
Mitogen-activated protein kinase (MAPK) 202, 234
Mitomycin 300, 303, 304
MMS technique 115
Moderating apoptosis 84
Modulating signal transduction pathways 99
Mohs micrographic surgery (MMS) 113, 115
Molecular 380, 383, 385, 387, 388, 389
 chaperone 383
 dynamics simulations (MDS) 380, 385, 387, 389
 modeling process 389
 targeted therapies 388
Molecular docking 287, 383, 385, 382, 386, 387
 method 386, 387
 technique 382
MOLEGRO software 384
Momordica charantia 205, 255, 382
Moringa oleifera 152, 244
Mucocutaneous cancers 115, 116, 119
 advanced 116
 diverse 115
 targeted therapeutic agents attack 119
Mucocutaneous tumour 125, 126
Mucosa 112, 113
 genital 113
 nasal 113
 oral 112
Mucosal melanomas 113
Mucositis 122, 116
 oral 122
Multi-drug resistance (MDR) 22, 302, 386
Multiple myeloma 272
Mutagenesis, targeted 353
Mutations 86, 87, 89, 114, 119, 200, 231, 299, 304, 306, 309
 bacterial 299, 309
 changing environmental conditions 309
 genetic 200, 231
Mycobacterium tuberculosis 173, 301, 308

Therapeutic Use of Plant Secondary Metabolites 419

N

Nanomedicine 40, 239, 269
Nanoparticle(s) 238, 240, 253, 257, 258, 259, 269, 270, 273, 274, 277, 278, 279, 280, 281, 282, 286, 287, 288, 289, 290, 291
 algae-mediated 277
 characterization techniques 280
 chitosan-curcumin 287
 green-synthesized antihyperglycemic 253
 metallic 257, 279, 290, 291
Nanoparticle synthesis 244, 258, 269, 270, 271, 277, 279, 286, 288, 290
 mediated green silver 286
 metallic 290
 plant-mediated silver 269
Nanophytomedicine 23
Nanosensors 239
Nanostructures 238, 251, 258, 291
 biocompatible 291
 green-synthesized 238, 258
 plant-synthesized 251
Nasturtium officinale 248
Natural 71, 151, 215
 antioxidants 71, 215
 detergents 151
 plant chemicals 215
Natural products 21, 22, 24, 26, 34, 35, 36, 139, 140, 141, 146, 147, 148, 214, 371
 plant-based 371
Natural stilbenes 99
Nausea 243, 289, 324
Neck cancer 379
Neisseria gonorrhoeae 299
Nephropathy 6, 9, 203, 242
 diabetes-induced 6
 diabetic 9
Nephrotoxic effects 333
Nervous system 219, 224
Networks 112, 355
 metabolic profiling correlation reaction 355
 papillary micro-vascularization 112
Neurodegeneration 215, 222, 233, 235

Neurodegenerative diseases 215, 229, 231, 233
 inherited 231
 multifactorial 229
 pathophysiology of 215, 233
 Neurodegenerative disorders 214, 222, 223, 235
 Neurogenesis 219
 Neuroinflammatory response 234
 Neuroprotective 6, 50, 217, 218, 220, 223
 activity 6
 effects 50, 217, 220, 223
 phenolic substances 218
 property 218
 Neurotoxicity 122
 Neurotransmitters 187, 219
 Next-generation sequencing 348
 Nicotinamide phosphoribosyl-transferase 379
Nigella sativa 103
 Nitrate reductase 277
 NMR-based spectroscopy 334
 Non communicable diseases (NCDs) 241
 Non-Hodgkin lymphomas 95
 Non-melanoma skin cancer (NMSCs) 112, 113, 115, 119, 121, 125, 126
 Non-melanoma skin cancer and melanoma 126
 Non-small cell lung cancer (NSCLC) 379
 Nuclear magnetic resonance (NMR) 29, 34, 37, 121, 332, 370, 375
 spectroscopy 375

O

Obesity condition 147
Ocimum 248, 256
basilicum 248, 256
sanctum 248, 256
 Oil 10, 50, 51, 53, 56, 69, 71, 72, 73, 75, 123, 125, 162, 165, 166, 216, 217, 218, 221, 222, 227, 228
 compounds, essential 69
 croton 71

essential (EOs) 50, 51, 53, 56, 69, 72, 73, 75, 162, 165, 166
 extraction process 53
 monoterpenoid 10
 mustard 228
 olive 216, 217, 218, 221
 palm 123, 125
 palm kernel 123, 125
 rice bran 123, 125
 seed 166
 vegetable 222, 227
 Omics 127, 323, 327, 235
 techniques 335
 technologies 127, 323, 327
 Oncolytic virotherapy 116
 Oral hypoglycaemic agents (OHAs) 242
 Organic stressors 312
 Organosulphur compounds 172
 Organ transplantations 194
Origanum majorana 50, 51, 53, 54, 55
 Osmotic shock 309
 Osteoarthritis 69
 Osteoporosis 222
 Oxidation 9, 52, 169, 218, 239, 299, 300, 302
 metal-dependent 300
 nucleotide 299
 Oxidative 89, 90, 140, 215, 218, 224, 226, 228, 234, 235, 244, 297, 298, 299, 304
 damage 228, 244
 stress 89, 90, 140, 215, 218, 224, 226, 234, 235, 297, 298, 299, 304
 Oxygen 72, 165, 257, 280, 302, 303, 304
 radical absorbance capacity (ORAC) 72

P

PAMP-triggered immunity (PTI) 174
 Pancreatic 12, 285, 288, 379
 cancer cell 285, 288
 carcinoma 379
 lipase 12
 Pancreatitis 203
Papaver 149, 186
rhoeas 149

Subject Index

somniferum 186
Parkinson's disease (PD) 215, 222, 223, 230, 231, 233
 neurotransmitter 231
Pathogenesis 69, 70, 71, 89, 230, 233, 234, 383, 388, 389
 neurodegenerative disease 389
Pathogenic 23, 148, 166, 168, 175, 215
 bacteria 148, 166, 175
 microbial infections 168
Pathogens 2, 3, 12, 141, 143, 145, 147, 148, 149, 151, 152, 153, 163, 171, 174, 304, 305, 307, 308
 drug-resistant priority 143
 microbial 2, 12, 163, 308
 virulence effectors 174
Pathways 3, 36, 37, 88, 89, 111, 118, 119, 120, 123, 150, 162, 164, 187, 190, 202, 203, 287, 302, 306, 309, 333, 345, 355
 amino acid metabolism 333
 apoptosis-signaling 88
 apoptotic 287
 biochemical 3, 36
 biosynthetic 3, 162, 190
 essential ribosomal 150
 haem synthesis 118
 insulin action 203
 intrinsic 88, 89
 mevalonic acid 187
 oxidative phosphorylation 302
 translocation 164
 tumour growth 119
Pelargonium graveolens 50, 51, 53, 54, 55
Penicillin 26, 70, 144, 369, 370
 natural 370
Penicillium 276
 brevicompactum 276
 fellutanum 276
Peptide(s) 139, 152, 164, 254, 271, 278, 354
 digested 354
 mass fingerprinting (PMF) 354
 milk-derived 152
 targeting 164
Peptidoglycan 172
Periodontitis 170

Therapeutic Use of Plant Secondary Metabolites 421

Peritonitis 70
Phosphokinases 98
Phospholipids 167, 300, 308
 polyunsaturated 300
Photooxidation 220
Photosynthesis 1
Phytochemicals 22, 97, 99, 118, 119, 120, 121, 221, 223, 257, 258, 259, 333, 344, 346, 383, 385
 nonflavonoid 99
 polyhydroxylated 97
Phytochemomics 323, 327, 333
 metabolomics Pharmacometabolomics 327
Phytonanotherapy 258
Phytonutrients 223, 224
Phytotherapy, omics concept in 327, 328, 329, 330, 331, 332, 334
Plant(s) 1, 2, 6, 7, 22, 23, 25, 26, 29, 30, 31, 40, 51, 52, 148, 151, 162, 165, 175, 187, 196, 204, 219, 241, 278, 305, 324, 329, 333, 335, 343, 344, 345, 346, 355, 357
 anodynes 324
 antimalaria 357
 aromatic 148
 based bioactive oligosaccharides 31
 bioactive compounds 30, 31
 castor oil 333
 crude 29
 dried 324
 ethnomedicinal 329, 335, 344, 345
 green tea 151
 medicine 40
 metabolites 22, 305, 333, 343, 346, 355
 peptides 333
 reproduction 2
 tissue repair 219
 traditional Chinese 31
Plasma membrane destabilization 141
Plasmodium 197
 knowlesi 197
 malariae 197
 ovale 197
Plasmodium falciparum 197, 199, 385
 lactate 199
Plectonema 277

- boryanum* 277
- terebrans* 277
- Polymerase chain reaction (PCR) 326, 328
- Polymeric chains 5
- Polymorphism ratio sequencing 348
- Polyols hydrolysis 168
- Polyphenolic 4, 97, 124, 189, 225
 - biomolecule 225
 - compounds 4, 97, 189
 - phytoalexin 124
- Polyphenols 1, 3, 141, 147, 148, 166, 221, 223, 224, 225, 245, 246, 249, 250, 255, 256
 - polymeric 225
- Pomegranates, castor oil 324
- Populations 84, 197, 230, 242, 310, 330, 334, 371
 - bacterial biofilm 310
 - tumour cell 84
- Porphyomonas gingivalis* 62, 64
- Postrate cancer 202
- Post-transcriptional processing 379
- Post-traumatic scars 114
- Preeclampsia 222
- Proanthocyanidins 5, 120, 168, 223
 - oligomeric 5
- Pro-apoptotic effects 330
- Procedures 28, 29
 - chromatography 29
 - pharmacognosy 28
- Processes 26, 27, 28, 34, 35, 36, 84, 85, 86, 87, 89, 103, 117, 122, 163, 164, 171, 348, 355, 371, 389
 - apoptotic 103
 - biochemical 36, 355
 - carcinogenic 86
 - pathogenic 122, 171
 - therapeutic 117
- Production 2, 3, 7, 8, 147, 216, 219, 243, 274, 275, 278, 304, 305, 306, 310, 351
 - antimicrobial peptides 147
 - biomass 275
 - glucagon 243
- Products 1, 35, 36, 38, 39, 166, 226, 241, 244, 333, 347, 355, 377
 - ligand-based medicinal 377
 - oxygen-producing 226
 - traditional medicinal 38
- Progress 84, 233, 370, 376, 388, 389
 - neurobiological 389
- Proinflammatory cytokines 118
- Properties 27, 35, 50, 70, 75, 162, 167, 168, 169, 170, 174, 195, 225, 226, 274, 279, 304, 351, 357, 377, 385
 - antifungal 167
 - anti-infectious 174
 - anti-inflammatory 70, 225, 304, 351
 - anti-microbial 162, 168, 170, 226
 - antioxidants and cytotoxicity 50, 75
 - antiparasitic 357
 - antiviral 195
- Prostaglandins, pro-inflammatory 217
- Prostate carcinoma cells 9
- Proteases 88, 89, 197, 220
- Proteasomes 220, 379
- Protection, toxic 226
- Protein(s) 9, 35, 86, 93, 95, 97, 104, 118, 121, 126, 164, 166, 171, 172, 241, 245, 247, 248, 249, 257, 259, 278, 279, 280, 300, 327, 330, 331, 344, 354, 380, 382, 383
 - anti-apoptotic 93, 104
 - brain cancer 383
 - diabetic 382
 - downregulating 121, 126
 - heat shock 9
 - inhibiting 118
 - metabolic 344
 - metabolism 241
 - mitosis-related 97
 - nuclear-encoded 164
 - penicillin binding 380
 - phosphorylation 330
 - survival-promoting 118
 - translation 331
 - tumour 95
 - tyrosine phosphatase 380, 382
- Protein kinase 100, 119, 234, 377
 - mitogen-activated 234
- Protein synthesis 95, 101, 150, 193, 215, 300, 301

Subject Index

aminoglycosides disrupt 300
inhibition 193
Proteolytic 25, 88, 152, 199
 cascade 88
 enzyme activities 152
Proteomics 34, 35, 323, 325, 328, 330, 331,
 343, 344, 345, 346, 347, 354, 378, 379
 applications 354
Proteostasis 231
Proteus vulgaris 57, 58, 61
Pseudolarix kaempferi 102
Pseudomonas 57, 58, 60, 61, 62, 63, 143, 144,
 169, 171, 276
 aeruginosa 57, 58, 60, 61, 62, 63, 143, 144,
 169, 171, 276
 stutzeri 276
Psidium guajava 168
Public health emergency 32
Pygeum africanum 325
Pyruvate dehydrogenase kinase (PDK) 379

Q

Quantitative structure activity relationships
(QSAR) 372, 377, 380, 384, 386

R

Radioimmunoassay 372
Radionecrosis 116
Radiotherapy 87, 114, 122, 200, 270
 stem cell transformation 200
Rapamycin 119, 200, 383
Rational drug design (RDD) 368, 369, 389
Reaction 72, 89, 152, 225, 279, 300, 301, 326,
 328, 330, 331, 355
 enzymatic browning 225
 haemolytic 152
 hydrogen transfer 72
 oxidative 301
 oxidative chain 89, 300
 polymerase chain 326, 328
 single electron transfer 72
Reactive 302, 311

Therapeutic Use of Plant Secondary Metabolites 423

 organic moieties 311
 oxygen therapy (ROT) 302
Reactive oxygen species (ROS) 52, 89, 118,
 217, 233, 234, 273, 297, 298, 300, 302,
 303, 304, 307, 310, 311, 312
 scavenger 217
Receptor tyrosine kinases 98
Reduction 238, 240, 245, 246, 247, 248, 249,
 250, 254, 255, 256, 257, 278, 279, 304
 flavoprotein-mediated one-electron 304
Regulating cell cycle and apoptosis 203
 pathways 203
Regulation 38, 41, 89, 93, 126, 146, 153, 200,
 204, 224, 225, 241
 herbal drug 38
 immune 146
Regulators 6, 70, 100
 essential 70
Regulatory genes 353
Rehmannia glutinosa 285
Replication 92, 169, 195, 196, 300, 309
 bacterial 309
 viral 195, 196
Resistance 84, 143, 144, 145, 152, 191, 194,
 192, 239, 297, 302, 305, 307, 312
 amoxicillin 307
 daptomycin 145
 fluoroquinolone 144
 microbial 297, 305
 tumour 84
 viral 194
Respiration 1, 51, 305
 aerobic 305
Respiratory 194, 307
 diseases 307
 syndrome coronavirus 194
Reversible DNA changes 327
Rhodotorula 285, 288
 glutinis 285, 288
 mucilaginosa 285, 288
Ribonucleotide reductase 379
Ricin-based preparation 333
Ricinus communis 333
Risk, reduced cancer 227
RNA 170, 301, 329

- polymerase 170
 - synthesis inhibition 301
 - transcripts 329
 - ROS-lethality link 302
 - Rosmarinus officinalis* 50, 51, 53, 54, 55, 69
 - ROS 301, 300, 304, 309, 312
 - mediated cell killing 300
 - neutralization 309
 - producing antibacterial agents and test
 - bacteria cell 301
 - production by quinone-based antimicrobial agents 304
 - production in cells 300
 - suppressor 312
 - target proteins 300
- S**
- Saccharomyces cerevisiae* 67
 - Salmonella* 57, 58, 59, 60, 62, 63, 64, 276, 308
 - enterica* 57, 58, 59, 60, 62, 63, 64
 - typhi* 276, 308
 - Salmonellosis DNA Gyrase 380
 - Salvia cadmica* 148
 - Sambucus nigra* 196, 249, 256
 - Saponins 1, 7, 11, 12, 141, 151, 245, 247, 248, 249, 259
 - Saraca asoca* 249, 256
 - Sargassum* 249, 256, 277, 284
 - muticum* 277, 284
 - swartzii* 249, 256
 - SARS-CoV-2 spike glycoprotein and main protease enzyme inhibitors 387
 - Scanning electron microscopy 165, 250, 281
 - Scavenging enzymes 306
 - Scutellaria barbata* 285
 - Seaweeds 121, 126, 249, 290
 - edible 121
 - Secondary metabolites 1, 2, 3, 7, 51, 52, 103, 141, 161, 162, 165, 169, 171, 185, 187, 191, 195, 196, 197, 200, 204, 205
 - of plant products 195
 - plant-derived 103, 171
 - production of 2, 51
 - Severe 97, 194
 - acute respiratory syndrome 194
 - multiple organ toxicity 97
 - Sexually transmitted disease (STDs) 55, 299
 - Signal 89, 98, 311
 - transducing kinases 98
 - transduction 89, 311
 - Signaling molecules, proinflammatory 8
 - Signalling pathways 121, 202
 - targeting numerous 121
 - Silybum marianum* 249
 - Sinensis 205, 332
 - schisandra 332
 - Skin 6, 112, 113, 118, 123, 127, 148, 151, 227, 250, 282, 325
 - disease 325
 - healthy 227
 - melanoma 123
 - transitions 112
 - Skin cancer 112, 113, 114, 119, 121, 123, 124, 125, 126, 127, 203, 383
 - non-melanoma 112, 113, 119, 125, 126
 - protein 383
 - treatment of 114, 121
 - Software, computer docking 384
 - Sol gel process 240
 - Solvents, toxic 241
 - Sources 21, 24, 25, 26, 36, 37, 51, 98, 99, 100, 121, 186, 187, 197, 215, 224, 225, 227, 299, 343, 356, 366, 368, 369, 371
 - heterogeneity 356
 - marine 100
 - natural 26, 37, 121, 197, 366, 368, 369, 371
 - of oxidative stress 299
 - Spanish sage thyme 188
 - Spectroscopic techniques 29
 - Spectroscopy 37, 250, 333
 - diffuse reflectance 250
 - dispersive 250
 - infrared 250
 - Squamous cell carcinomas (SCC) 112, 114
 - Staphylococcus aureus* 57, 58, 59, 60, 61, 62, 63, 144, 148, 150, 151, 152, 166, 172, 193

Subject Index

methicillin-resistant 144, 150, 151, 152
Stem cells 373, 374
 human-induced pluripotent 374
 human pluripotent 373
 inducible pluripotent 373, 374
 intestinal 373
Steroidal 69, 174
 drugs 69
 glycoalkaloids 174
Stimulate 146, 243, 373
 defence mechanisms 146
 emission depletion (STED) 373
 insulin secretion 243
Streptococcus 12, 60
 faecalis 12
 pyogenes 60
Streptomycin 70
Stress 52, 88, 99, 124, 187, 298, 304, 308,
 309, 324
 biotic 187
 mediated endoplasmic reticulum 124
Stressor 309, 311
 metabolic 311
Stroke 214, 215, 222, 223, 232, 233, 235, 304
 ischemic 233
Structure-based high-throughput screening
 (SBHTS) 377
Sulphonyl ureas 243
Supercomputing system 347, 357
 high-performance 357
Superoxide 89, 100, 220, 305, 306, 310
 dismutase 89, 100, 220, 306, 310
 radicals 306
Supplementation 219, 308
 nutritional 219
Suppression 6, 8, 69, 103
 tumor growth 103
Surface plasmon resonance (SPRs) 271, 279
Surgical excision of mucocutaneous cancers
 115
Syzygium cumini 257
Synergistic effect 287, 330, 371
Synthesis 2, 3, 29, 167, 171, 172, 216, 238,
 239, 240, 241, 245, 246, 247, 274, 275,
 278, 291, 301, 368, 384

Therapeutic Use of Plant Secondary Metabolites 425

 cryo-chemical 274
 extracellular enzyme 167
 green biological 241
 inhibition 301
 microbe-mediated 278
 mutant 216
 organic 368
 plant-mediated 278
Synthesized nanoparticles 279, 282
 metal-green 282
Syngonium isoetifolium 249
System 89, 240, 241, 288, 308, 323, 327, 328,
 330, 331, 332, 334, 344, 353, 354, 356,
 374
 active transport 308
 allopathic 344
 anti-oxidant 89
 gene editing 374
 renal glomerular 288
Systemic acquired resistance (SAR) 174
Syzygium 173, 249
 aromaticum 173
 cumini 249

T

Taraxacum officinale 284, 287
Targeted mucocutaneous cancer therapies 117
Targeting 88, 164
 anti-cancer drugs 88
 peptide (TPs) 164
Target 174, 303, 305, 283
 efflux pump inhibitors 174
 microbial cells 303, 305
 microorganism 305
 proteins 383
Taxonomics 350, 351
TCA pathway 302
Tea 8, 9, 99, 124, 126, 221
 black 9
 green 8, 99, 124, 126, 221
Techniques 29, 35, 36, 37, 91, 118, 240, 274,
 277, 279, 281, 298, 325, 326, 328, 331,
 333, 335, 344, 353, 372, 383, 389

- biomarker-oriented 389
- chemical 91
- computational biology 372
- high-throughput 298, 353
- microscopic 240
- molecular biology 344
- non-chromatographic 29
- quantum chemistry 383
- Technologies 37, 291, 328, 375, 389
 - green 291
 - imaging 389
 - microfluidic 37, 375
 - next-generation genomic 328
- Telangiectasia 116
- Tephrosia* 250, 257, 387
 - tinctoria* 250, 257
 - catappa* 387
- Therapeutic agents 21, 32, 39, 270, 271, 323, 328, 332, 343, 344, 347
- Therapeutic effects 7, 38, 75, 123, 139, 145, 187, 222, 289
 - broad-spectrum 139, 145
- Therapeutic Intervention 115, 116
 - conventional 115, 116
 - surgical 115
- Therapy 13, 91, 93, 114, 116, 117, 119, 122, 139, 140, 145, 175, 200, 238, 258, 270, 271, 302, 306, 307, 308, 323, 333, 369, 370
 - adjuvant treatment 113
 - antibiotic 145
 - cancer nanoparticle 270
 - conventional 238, 271
 - herbal 258, 323, 333
 - immunomodulatory 116
 - leukemia 271
 - photodynamic 114, 117, 200
 - plant-based anti-microbial 175
 - radiation 116
 - reactive oxygen 302
- Thermogravimetric analysis 250
- Thin layer chromatography 29
 - high-performance 29
- Thioredoxin reductase 170
- Threat 35, 144, 194, 216, 234, 386
 - distressing 194
- Thrombosis 31, 69
- Thymidine synthesis 379
- Thymus vulgaris* 50, 52, 53, 54, 55, 165, 171, 172, 194
- Tinospora cordifolia* 166
- Tissues 71, 73, 85, 86, 89, 113, 118, 224, 323, 330, 331, 334, 354, 355
 - fastest-growing 85
 - reduced granulomatous 71
- Tolypocladium inflatum* 24
- Tools 112, 326, 333, 357
 - biochemical profiling 333
 - bioinformatics data mining 357
 - omics-based theragnostic 112
 - repository 326
- Toxic cytokine 124
- Toxicity 38, 39, 55, 117, 122, 250, 251, 253, 254, 255, 256, 257, 260, 306, 367, 368, 369, 370
 - dermatological 117
 - gastrointestinal 122
 - reduced 306
- Toxicogenomics 323, 328
- Toxicometabolomics 323, 332, 333
- Toxicoproteomics 331
- Traditional 21, 23, 50, 51, 52, 165, 323, 326, 331, 334, 343, 344, 346, 353, 369, 372
 - and complementary medicine (TCM) 32, 165
 - medicine 21, 23, 50, 51, 52, 323, 326, 331, 334, 343, 344, 346, 353
 - techniques of drug discovery 369
 - toxicity assessment 372
- Transcriptome 327, 353
- Transcriptomic 329
 - database profile 329
 - profile 329
- Transferases 89
- Transformation 114, 120, 331
 - malignant 120
 - neoplastic 114
- Transmission electron 240, 250, 281
 - microscopy 250, 281
- Treatment 100, 116, 119, 170, 186, 197

Subject Index

malaria 170, 197
methods 119
radiation 116
solamargine 100
therapeutic 186
Treponema pallidum 299
Trichoderma asperellum 276
Trichophyton 65, 68, 149
 mentagrophytes 65, 68
 rubrum 149
Trigonella foenum 250
Tripterygium wilfordii 333
Trolox equivalent antioxidant capacity
 (TEAC) 72
Trypanosoma brucei 40
Tuberculosis 39, 55, 166, 301, 304, 310
Tubulin depolymerization effects 94
Tumor 30, 31, 87, 117, 200, 204, 272, 375,
 382
 mass 87
 necrosis 204
 relapse 117
 solid 375
 resistance 117
 suppressors 382
Tumor cell 101, 123
 apoptosis 101
 proliferation 123
Tumour cell 101
 apoptosis 101
 proliferation 101
Tyrosine kinases 9, 98, 379

U

UDP 217, 353
 dependent glycosyltransferases 353
 glucuronosyltransferase 217
Ulcers 6, 71, 114, 242
 chronic 114
 reduced 71
Ultra-performance liquid chromatography 334
Ultraviolet 113, 187, 281
 radiation 113, 187

Therapeutic Use of Plant Secondary Metabolites 427

Visible Spectrophotometry 281
Urinary tract infection 55, 243, 303, 380
 Penicillin binding protein 380
UVB-induced skin cancer 124
UV-visible Spectrophotometry 279

V

Vaccines 23, 217, 366
 traditional 23
Vaginal cavities 70
Vancomycin resistant Enterococci (VRE) 145
Vascular endothelial growth factor (VEGF)
 100, 202, 271, 272, 273, 383, 384
Verbena officinalis 387
Vibrio cholera 276
Viral 10, 147, 194, 205, 299, 381, 386
 diseases 10, 194, 205
 epidemics 194
 infection 147, 194, 299, 381, 386
Virus 10, 194, 195, 196, 299
 chikungunya 195
 dengue 195
 herpes 194, 195
 human immunodeficiency 195, 299
 severe acute respiratory syndrome corona 10
Vomiting 243, 289

W

Wasabia japonica 228
Water 2, 3, 89, 222, 224, 225, 226, 241, 247,
 249, 250, 306
 based tannins 225
Water-soluble 256, 333
 glycoprotein 333
 heterocyclic compounds 256
Western blot analysis 288
World Health Organization (WHO) 6, 25, 32,
 33, 34, 91, 143, 144, 165, 191, 244

X

Xanthophylls 226

Xenobiotics 9

X-ray 238, 239, 240, 245, 246, 247, 248, 249,
250, 280, 281

diffraction (XRD) 238, 240, 245, 246, 247,
248, 249, 250, 280, 281

diffractometer 250

imaging 239

photoelectron spectroscopy 250, 281

XRD techniques 280

Z

Zika virus 195

Zinc oxide 26, 238, 239, 245, 246, 247, 248,
249, 250, 259, 282, 283, 284, 285

Zingiber officinale 250

Zoopharmacognosy 26