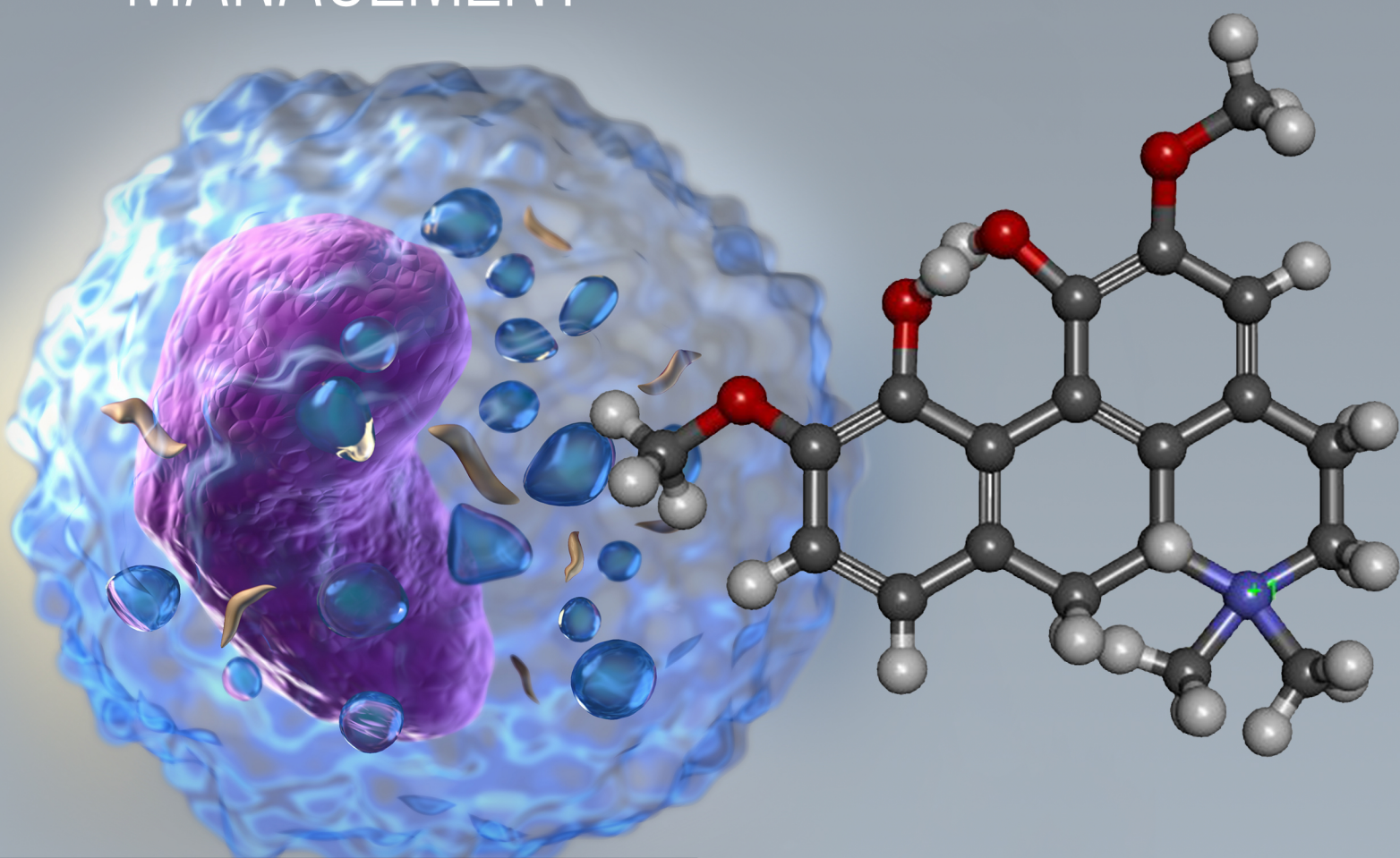


NATURAL IMMUNOMODULATORS: PROMISING THERAPY FOR DISEASE MANAGEMENT



Editors:
Vandana S. Nikam
Sujata P. Sawarkar
Girish B. Mahajan
Supriya G. Jagtap

Bentham Books

Natural Immunomodulators: Promising Therapy for Disease Management

Edited By

Vandana S. Nikam

*Department of Pharmacology, STES's Smt. Kashibai Navale
College of Pharmacy, S. P. Pune University, Pune 411048,
Maharashtra, India*

Sujata P. Sawarkar

*SVKM's Dr. Bhanuben Nanavati College of Pharmacy,
V. M. Road, Mumbai University, Mumbai 400056,
Maharashtra, India*

Girish B. Mahajan

*HiMedia Laboratories Pvt Ltd., Mumbai 400604,
Maharashtra, India*

&

Supriya G. Jagtap

*Department of Pharmacognosy, STES's Smt. Kashibai Navale
College of Pharmacy, S. P. Pune University, Pune 411048,
Maharashtra, India*

Natural Immunomodulators: Promising Therapy for Disease Management

Editors: Vandana S. Nikam, Sujata P. Sawarkar, Girish B. Mahajan & Supriya G. Jagtap

ISBN (Online): 978-981-5123-25-8

ISBN (Print): 978-981-5123-26-5

ISBN (Paperback): 978-981-5123-27-2

© 2023, Bentham Books imprint.

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

First published in 2023.

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

PREFACE 1	i
PREFACE 2	ii
LIST OF CONTRIBUTORS	iii
CHAPTER 1 INTRODUCTION: IMMUNE SYSTEM & MODULATION OF IMMUNE SYSTEM	1
<i>Manali S. Dalvi, Sanjay D. Sawant and Vandana S. Nikam</i>	
INTRODUCTION	1
COMPONENTS OF THE IMMUNE SYSTEM	2
Bone Marrow	3
Thymus	4
Lymph Node	4
Spleen	5
IMMUNE SYSTEM IS COMPOSED OF TWO MAIN COMPONENTS, NAMELY	5
Innate Immunity	6
Anti-microbial Substance	6
<i>Interferons</i>	6
<i>Iron Binding Proteins</i>	7
<i>Anti-Microbial Proteins (AMP)</i>	7
<i>Complement</i>	8
Phagocytes	10
Natural Killer Cells	11
Mechanism of the Innate Response	12
Cell Involve in Innate Immunity	12
<i>Granulocytes</i>	13
<i>Macrophages and Mast Cells</i>	14
<i>Dendritic Cells</i>	14
Adaptive Immunity	15
Major Histocompatibility Complex Antigens	16
Clonal Selection	17
<i>Cell-Mediated Response</i>	18
<i>Activation of T Cells</i>	18
<i>Humoral Response</i>	20
Activation of B Cells	21
Immunological Memory	21
ALLERGY AND HYPERSENSITIVITY REACTION	21
Classification of Hypersensitivity Reactions	22
<i>Type I Hypersensitivity Reaction Fig.(10)</i>	23
<i>Type II Hypersensitivity Reaction</i>	24
<i>Type III Hypersensitivity Reaction</i>	26
<i>Type IV Hypersensitivity Reaction</i>	26
IMMUNOMODULATION	28
Microbiota and Prebiotic, Probiotics	29
Micronutrients	30
Natural Health Products	31
Vaccines	31
IMMUNOTHERAPY	32
CONCLUSION	33
CONSENT FOR PUBLICATION	34

CONFLICT OF INTEREST	34
ACKNOWLEDGEMENTS	34
REFERENCES	34
CHAPTER 2 DISEASES AND DISORDERS ASSOCIATED WITH IMMUNE SYSTEM	41
<i>Pooja Shimpi, Smita Pillewan and Vandana S. Nikam</i>	
INTRODUCTION	41
CLASSIFICATION OF IMMUNE DISEASES AND DISORDERS	42
BROAD CLASSIFICATION OF IMMUNE DISEASES AND DISORDERS	42
Immunodeficiencies (IDs)	42
Classification of Immune Diseases and Disorders Based on Inborn Errors of Immunity	43
Phenocopies of Inborn Errors of Immunity	46
<i>X-linked Agammaglobulinemia</i>	46
<i>Wiskott–Aldrich Syndrome (WAS)</i>	46
<i>Ataxia Telangiectasia (A-T)</i>	47
<i>DiGeorge Syndrome</i>	47
Secondary Immunodeficiency Disorders	47
Allergic/ Hypersensitivity Reactions	48
<i>Allergic Rhinitis</i>	49
<i>Atopic Eczema/ Atopic Dermatitis</i>	49
<i>Urticaria</i>	51
<i>Stevens-Johnson Syndrome</i>	52
Autoimmune Disorders	53
CLASSIFICATION OF IMMUNE DISEASES BASED ON ORGAN SPECIFICITY	55
ORGAN-SPECIFIC (LOCALIZED) DISEASES FIG. (3)	56
Endocrinologic Diseases	56
<i>Hashimoto’s (autoimmune) thyroiditis</i>	56
Neurological Disorders	57
<i>Introduction</i>	57
<i>Alzheimer’s Disease and Parkinson’s Disease</i>	58
<i>Multiple Sclerosis</i>	59
Auto-inflammatory Diseases/ Systemic Autoinflammatory Diseases (SAIDs)	60
<i>Introduction</i>	60
<i>Classification Of Auto-Inflammatory Diseases</i>	61
<i>Monogenic Autoinflammatory Diseases</i>	61
<i>Polygenic Autoinflammatory Diseases</i>	64
ROLE OF THE IMMUNE SYSTEM IN CANCER	65
IMMUNE CELLS AND CANCER PROGRESSION	65
CONCLUSION	68
CONSENT FOR PUBLICATION	68
CONFLICT OF INTEREST	69
ACKNOWLEDGEMENTS	69
REFERENCES	69
CHAPTER 3 NATURAL SOURCES OF IMMUNOMODULATORS	75
<i>Vishal Bhange, Monika Kale, Ankita Dudhal, Nikhil Putta, Mukta Abhyankar,</i>	
<i>Supriya Jagtap and Vandana S. Nikam</i>	
INTRODUCTION	75
PLANTS AS SOURCE OF IMMUNOMODULATORS	77
Glycosides	77
Tannins	77
Coumarins	78

Anthocyanins	78
Saponins	78
Alkaloids	79
Volatile Oils and Terpenoids	79
MARINE-DERIVED IMMUNOMODULATORS	83
Immunomodulatory Compounds from Marine Origin	84
MICROBIOTA MODIFIERS	85
Prebiotics	85
Fructans (Fructo-oligosaccharide or FOS)	85
β -Glucan	86
<i>Role of β-glucan Structure</i>	86
Probiotic	86
<i>Probiotic Augmentation Method in the Immune System</i>	87
<i>Mechanism of Action of Probiotics</i>	87
VACCINES	90
Jennerian Vaccines	90
Live-attenuated Vaccines	91
Inactivated Vaccines	91
Toxoids	91
Subunit, Recombinant, Polysaccharide, and Conjugate Vaccines	92
Combination of Vaccine	92
Messenger RNA (mRNA) Vaccines	92
IMMUNOADJUVANTS	92
MICRONUTRIENTS	94
Vitamin A	94
Vitamin C	96
Vitamin D	97
Vitamin B	99
Vitamin E	99
TRACE ELEMENTS	100
Essential Elements	100
<i>Zinc</i>	100
<i>Selenium</i>	101
<i>Copper</i>	102
<i>Omega-3 Fatty Acid</i>	102
CONCLUDING REMARKS	103
CONSENT FOR PUBLICATION	103
CONFLICT OF INTEREST	103
ACKNOWLEDGEMENTS	103
REFERENCES	103
CHAPTER 4 STANDARDIZATION OF IMMUNOMODULATOR NATURAL DRUGS	108
<i>Aishwarya R. Nale and Supriya G. Jagtap</i>	
INTRODUCTION	109
NEED FOR DRUGS FROM PLANT ORIGINS OVER SYNTHETIC DRUGS	110
STANDARDIZATION OF DRUGS FROM NATURAL ORIGINS	112
Need for Standardization: Producers' and Consumers' Outlook	113
Standardization of Natural Drugs Using Marker Compound Analysis	114
Processes and Procedures for Standardisation and Quality Control of Natural Drugs are	
Described	116
<i>Authentication</i>	117

<i>Foreign Matter</i>	117
<i>Organic Evaluation</i>	117
<i>Microscopy</i>	117
<i>Volatile Matter</i>	117
<i>Ash Value</i>	117
<i>Extractive Values</i>	118
<i>Chromatographic Profile of Marker Compound</i>	118
<i>Pesticide Residues</i>	118
<i>Determination of Heavy Metals</i>	119
<i>Microbial Contamination</i>	119
<i>Radioactive Contamination</i>	119
Current Natural Drug Standardization Regulations	119
IMMUNOMODULATING PLANT DRUGS	122
Importance of Natural Immunomodulators	122
Ayurveda Concept	122
PLANT TISSUE CULTURE	129
Advantages of Plant Tissue Culture for Standardization of Phytoconstituents	130
STANDARDIZATION OF NATURAL IMMUNOSTIMULANTS	130
A. <i>Tinospora Crispa</i>	130
<i>Description</i>	130
<i>Collection and Extraction</i>	130
<i>Standardization</i>	130
<i>Immunomodulatory Assays</i>	131
Results	132
<i>Standardization</i>	132
<i>Immunomodulatory Assays</i>	133
B. <i>Mangifera Indica & Curcuma Domestica</i>	133
<i>Description</i>	133
<i>Collection and Extraction</i>	133
<i>Phytochemical Screening</i>	133
<i>Standardization</i>	133
<i>Immunomodulatory Assays</i>	134
Results	135
<i>Phytochemical Screening</i>	135
<i>Standardization</i>	135
<i>Immunomodulatory Assays</i>	136
C. <i>Stereospermum Suaveolens</i>	136
<i>Description</i>	136
<i>Collection and Extraction</i>	136
<i>Phytochemical Analysis</i>	136
<i>Standardization</i>	136
<i>Immunomodulatory Assays</i>	137
Results	137
<i>Phytochemical Analysis</i>	137
<i>Standardization</i>	137
<i>Immunomodulatory Assays</i>	137
D. <i>Barleria Prionitis</i>	138
<i>Description</i>	138
<i>Collection and Storage</i>	138
<i>Extraction</i>	138
<i>Phytochemical Screening</i>	138

<i>Standardization</i>	138
<i>Immunomodulatory Assays</i>	139
Results	140
<i>Phytochemical Screening</i>	140
<i>Standardization</i>	140
<i>Immunomodulatory Assays</i>	140
STANDARDIZATION OF NATURAL IMMUNOSUPPRESSANTS	140
A. <i>Phyllanthus Amarus</i>	140
<i>Description</i>	140
<i>Collection and Extraction</i>	141
<i>Standardization</i>	141
<i>Immunomodulatory Assays</i>	142
Results	142
<i>Standardization</i>	142
<i>Immunomodulatory Assays</i>	143
B. <i>Zingiber Zerumbet</i>	144
<i>Description</i>	144
<i>Collection and Extraction</i>	144
<i>Standardization</i>	144
<i>Reversed-phase HPLC</i>	144
<i>LC-MS/MS</i>	146
<i>Immunomodulatory Assays</i>	146
Results	147
<i>RP-HPLC</i>	147
<i>LC-MS/MS</i>	147
<i>Immunomodulatory Assays</i>	148
C. <i>Momordica Charantia</i>	148
<i>Description</i>	148
<i>Collection, Extraction and Standardization</i>	149
<i>Immunomodulatory Assays</i>	149
Results	150
<i>Standardization</i>	150
<i>Immunomodulatory Assays</i>	150
D. <i>Terminalia Chebula</i>	150
<i>Description</i>	150
<i>Collection, Extraction and Standardization</i>	151
<i>Immunosuppressive Effect as an Anti-arthritic Treatment</i>	151
Results	152
<i>Standardization</i>	152
<i>Immunosuppressive and Anti-arthritic Effects</i>	152
STANDARDIZATION OF IMMUNOMODULATING TISSUE CULTURED PLANTS	152
<i>Echinacea Angustifolia</i>	152
<i>Description</i>	152
<i>Cell Culture Formation & Extraction</i>	153
<i>Standardization</i>	153
<i>Immunomodulatory Assays</i>	153
<i>Helicteres Angustifolia</i>	154
<i>Description</i>	154
<i>Extraction of Callus Suspension Cultures</i>	154
<i>Standardization</i>	154
<i>FTIR Analysis</i>	154

<i>Phytochemical Screening</i>	154
<i>Quantitative Analysis</i>	155
<i>HPLC Analysis</i>	155
<i>Immunomodulatory Assays</i>	156
RESULTS	156
Standardization	156
<i>Ftir Analysis</i>	156
<i>Phytochemical Screening</i>	156
<i>Quantitative Analysis</i>	157
<i>HPLC Analysis</i>	157
<i>Immunomodulatory Assays</i>	158
CONCLUDING REMARKS	158
CONSENT FOR PUBLICATION	159
CONFLICT OF INTEREST	159
ACKNOWLEDGEMENTS	159
REFERENCES	159
CHAPTER 5 IMMUNOMODULATORS: CHEMISTRY AND ANALYTICAL TECHNIQUES	165
<i>Akalya Sendrayakannan and Prashant S. Kharkar</i>	
INTRODUCTION	165
IMMUNOMODULATORS	166
Immunomodulators from Natural Sources	168
PHYTOCHEMICALS AS IMMUNOMODULATORS	171
Emodin	171
Quercetin	172
Resveratrol	175
Genistein	177
SEARCH FOR NEWER, SAFER IMMUNOMODULATORS	178
ANALYTICAL TECHNIQUES FOR ISOLATION, PURIFICATION, QUANTIFICATION AND CHARACTERIZATION OF NATURAL IMMUNOMODULATORS	178
Chromatography	180
<i>High-Performance Liquid Chromatography (HPLC)</i>	180
<i>High-Performance Thin Layer Chromatography (HPTLC)</i>	180
<i>Droplet Counter-Current Chromatography (DCCC)</i>	180
<i>High-Speed Counter-Current Chromatography (HSCCC)</i>	181
High-Performance Capillary Electrophoresis (HPCE)	181
Spectroscopy	181
<i>Ultraviolet/Visible (UV/Vis) Spectroscopy</i>	182
<i>Fourier-Transform Infra-Red (FT-IR) Spectroscopy</i>	182
<i>Mass Spectrometry (MS)</i>	182
<i>Nuclear Magnetic Resonance (NMR) Spectroscopy</i>	182
BIOACTIVITY SCREENING METHODS FOR THE IMMUNOMODULATORS	182
CONCLUDING REMARKS	184
CONSENT FOR PUBLICATION	184
CONFLICT OF INTEREST	184
ACKNOWLEDGEMENTS	184
REFERENCES	184
CHAPTER 6 BIOASSAYS AND OTHER METHODS FOR IMMUNOMODULATORS IN PRECLINICAL AND CLINICAL SETTING	189
<i>Priyanka P. Nigade, Pranjali S. Dhamane and Vandana S. Nikam</i>	
INTRODUCTION	189

ASSOCIATION OF INNATE IMMUNITY AND ADAPTIVE IMMUNITY AND THEIR MEASUREMENTS	190
Screening of Immunomodulators	192
Animal Models used for Immunomodulatory Studies	193
PRECLINICAL EVALUATION FOR IMMUNOMODULATORS	193
CELL CULTURE	193
IN VITRO METHODS FOR IMMUNOMODULATORS EVALUATION	193
Inhibition of Histamine Release from Mast Cells [20 - 22]	195
Mitogen-Induced Lymphocyte Proliferation /T Cell Proliferation Assay [17, 20, 23, 24]	196
Inhibition of T Cell Proliferation [20]	197
Phagocytosis Evaluation	197
<i>Chemiluminescence in Macrophages [20]</i>	197
<i>Polymorphonuclear (PMN) Leucocyte's Function Test using Candida Albicans Spores [25, 26]</i>	197
PFC (Plaque Forming Cell) Assay [27]	198
Inhibition of Dihydro-Orotate Dehydrogenase [20]	198
MTT Assay & Cyclic Voltammetry for Cell Viability and Proliferation	199
Cytokine ELISA and Biological Assay [31]	199
Nitrite Determination using Colorimetric Griess Reaction Assay [32]	200
Nitro-blue tetrazolium (NBT) Reduction Assay [33]	200
Myeloperoxidase Activity Assay [33]	200
A Flow Cytometry-Based Assay for Natural Killer Cell Activity Evaluation	201
IN VIVO METHODS FOR IMMUNOMODULATORS EVALUATION	201
Assessment of Cellular Immunity	202
<i>Carbon-Clearance Test for Determination of Macrophage Phagocytic Index [35]</i>	202
<i>Neutrophil Adhesion Test [36]</i>	203
Hypersensitivity Reaction [16]	203
Reversed Passive Arthus (RPA) Reaction [37]	204
Assessment of Humoral Immune Immunity [38]	204
<i>Hemagglutination Antibody Titer Test</i>	204
<i>Mice Lethality Test</i>	204
Determination of Immune Organ Index in Mice [35, 39]	205
Determination of Serum Hemolysin Level in Mice [35]	205
Systemic Anaphylaxis in Mice [40, 41]	205
Adjuvant Arthritis in Rats [42]	206
Collagen Type II Induced Arthritis in Rats [43]	207
Experimental Autoimmune Thyroiditis [44]	207
SPONTANEOUS AUTOIMMUNE DISEASE IN ANIMALS [20]	208
Anti-anaphylactic Activity (Schultz-Dale Reaction) [45]	208
Proteoglycan-Induced Progressive Polyarthritis in Mice [46]	209
Coxsackievirus B3-Induced Myocarditis [47]	209
Experimental Allergic Encephalomyelitis [20]	209
Prevention of Experimentally Induced Myasthenia Gravis in Rats [20]	209
Inhibition of Allogeneic Transplant Rejection [20]	210
Influence on SLE-like Disorder in MRL/lpr Mice [48, 49]	210
CONCLUSION	211
CONSENT FOR PUBLICATION	212
CONFLICT OF INTEREST	212
ACKNOWLEDGEMENTS	212
REFERENCES	212

CHAPTER 7 NATURAL IMMUNOMODULATORS IN CANCER THERAPY	216
<i>Chaitrali Shevkar and Abhijeet S. Kate</i>	
INTRODUCTION	216
Curcumin	220
Resveratrol	221
Quercetin	222
Genistein	223
Betulinic Acid	224
Zerumbone	225
Berberine	226
Epigallocatechin Gallate	227
Miscellaneous	228
CONCLUDING REMARKS	231
CONSENT FOR PUBLICATION	231
CONFLICT OF INTEREST	231
ACKNOWLEDGEMENTS	232
REFERENCES	232
CHAPTER 8 NATURAL IMMUNOMODULATORS FOR INFECTIONS AND OTHER DISEASES	243
<i>Aaliya Liyakath Ali, Namrata Nailwal, Sujata Sawarkar and Gaurav Doshi</i>	
INTRODUCTION	243
INFECTIOUS DISEASES	244
Curcumin	247
<i>Antibacterial Activity</i>	247
<i>Antifungal Activity</i>	247
<i>Argyrea Speciosa</i>	248
<i>Antibacterial Activity</i>	248
<i>Antifungal Activity</i>	248
<i>Antiviral Activity</i>	248
<i>Antiparasitic Activity</i>	249
<i>Mangifera Indica</i>	249
<i>Antiviral Activity</i>	249
<i>Antiparasitic Activity</i>	249
<i>Antibacterial And Antifungal Activities</i>	249
<i>Tinospora Sinensis</i>	250
<i>Antimicrobial Activity</i>	250
<i>Antiviral Activity</i>	250
<i>Trigonella Foenum-gracium</i>	250
<i>Antifungal Activity</i>	250
<i>Antibacterial Activity</i>	251
<i>Antiparasitic Activity</i>	251
<i>Platycodon Grandiflorum</i>	251
<i>Antimicrobial Activity</i>	251
<i>Antiviral Activity</i>	251
Resveratrol	252
<i>Antibacterial Activity</i>	252
<i>Antifungal Activity</i>	252
<i>Antiparasitic Activity</i>	252
<i>Antiviral Activity</i>	252
Epigallocatechin-3-Gallate	253

<i>Antibacterial Activity</i>	253
<i>Antiviral Activity</i>	253
<i>Antifungal Activity</i>	253
<i>Antiparasitic Activity</i>	253
Genistein	254
<i>Antibacterial Activity</i>	254
<i>Antiviral Activity</i>	254
<i>Antiparasitic Activity</i>	254
Quercetin	254
<i>Antibacterial Activity</i>	255
<i>Antifungal Activity</i>	255
<i>Antiparasitic Activity</i>	255
<i>Antiviral Activity</i>	255
Colchicine	255
<i>Antibacterial Activity</i>	256
<i>Antiviral Activity</i>	256
Capsaicin	256
<i>Antibacterial Activity</i>	256
Andrographolide	256
<i>Antibacterial Activity</i>	257
<i>Antiviral Activity</i>	257
<i>Antiparasitic Activity</i>	257
<i>Tripterugium Wilfordii</i>	257
<i>Antibacterial Activity</i>	257
<i>Acorus Calamus</i>	257
<i>Antibacterial Activity</i>	258
<i>Antifungal Activity</i>	258
<i>Antiviral Activity</i>	258
<i>Antiparasitic Activity</i>	258
<i>Emblica Officinalis</i>	259
<i>Antibacterial Activity</i>	259
<i>Antifungal Activity</i>	259
<i>Antiviral Activity</i>	260
<i>Evolvulus Alsinoides</i>	260
<i>Antibacterial Activity</i>	260
<i>Antifungal Activity</i>	260
CONCLUSION	260
CONSENT FOR PUBLICATION	261
CONFLICT OF INTEREST	261
ACKNOWLEDGEMENTS	261
REFERENCES	261
CHAPTER 9 DELIVERY OF IMMUNOMODULATORS: CHALLENGES AND NOVEL APPROACHES	275
<i>Mansi Damani, Prabha Singh and Sujata Sawarkar</i>	
INTRODUCTION	275
NATURAL IMMUNOMODULATORS	277
CHALLENGES IN THE DELIVERY OF NATURAL IMMUNOMODULATORS	283
Standardization Challenges	283
Formulation Challenges	284
Administration Challenges	285

Regulatory Concerns	286
NOVEL APPROACHES FOR DELIVERY OF NATURAL IMMUNOMODULATORS	286
Nanoparticles	287
<i>Polymeric Nanoparticless</i>	287
<i>Mesoporous Silica Nanoparticles</i>	289
<i>Lipid Nanoparticles</i>	290
<i>Metal Nanoparticles</i>	293
Liposomes and Niosomes	294
Polymeric Micelles	296
Dendrimer	297
Nanoemulsion And Microemulsions	298
Transferosome	301
Ethosomes	302
CONCLUSION	307
CONSENT FOR PUBLICATION	307
CONFLICT OF INTEREST	307
ACKNOWLEDGEMENTS	308
REFERENCES	308
CHAPTER 10 MARKETING STRATEGY & REGULATORY PERSPECTIVE FOR NATURAL IMMUNOMODULATORS	323
<i>Alveera Ansari, Namrata Nailwal, Sujata Sawarkar and Gaurav Doshi</i>	
INTRODUCTION	324
UNITED STATES OF AMERICA (USA)	328
Drugs & Biological Products	329
INDIA	330
AUSTRALIA	331
UNITED KINGDOM	331
CANADA	332
EUROPE	334
DENMARK	335
NEW ZEALAND	336
IRELAND	336
BRAZIL	337
THAILAND	339
SWEDEN	341
ITALY	343
GERMANY	344
CHINA	345
SOUTH KOREA	347
SWITZERLAND	349
HONGKONG	350
FRANCE	351
NIGERIA	351
UGANDA	354
MALAYSIA	354
NETHERLANDS	355
SINGAPORE	356
JAPAN	357
GULF COUNTRIES (SAUDI ARABIA, KUWAIT, THE UNITED ARAB EMIRATES, QATAR, BAHRAIN, OMAN)	358

Regulatory Agencies of the Gulf Cooperation Council	358
Procedure for Centralised Registration	358
Procedure for Registration that is not Centralised	359
SOUTH AFRICA	359
Application Number	359
Electronic Entries	359
Models of Reliance	360
GMP	360
Document SCoRE	360
ARMENIA, AZERBAIJAN, BELARUS, GEORGIA, KAZAKHSTAN, KYRGYZSTAN, TURKMENISTAN, MOLDOVA, RUSSIA, TAJIKISTAN, UKRAINE, UZBEKISTAN (THE COMMONWEALTH OF INDEPENDENT STATES)	360
VIETNAM, THAILAND, SINGAPORE, PHILIPPINES, BRUNEI, CAMBODIA, INDONESIA, LAOS, MALAYSIA, MYANMAR (ASSOCIATION OF SOUTH ASIAN NATIONS)	361
CONCLUSION	362
CONSENT FOR PUBLICATION	362
CONFLICT OF INTEREST	362
ACKNOWLEDGEMENTS	363
REFERENCES	363
CHAPTER 11 NATURAL VS. SYNTHETIC IMMUNOMODULATORS	368
<i>Girish B Mahajan and Lakshmi Balachandran</i>	
INTRODUCTION	368
The Nature of the Immune Response	368
NATURAL IMMUNOMODULATORS (NI)	370
Rasayana [10]	370
CHEMICAL NATURE OF NATURAL IMMUNOMODULATORS	371
Propionibacterium Species as an Immunomodulator	372
Glucan	373
Curcumin [19]	373
Resveratrol	374
Glycosides [27]	375
Flavonoids [28]	375
Sapogenins	376
Alkaloids	376
Thiosulfates	376
Volatile Oils and Terpenoids [32]	377
MECHANISM OF NATURAL IMMUNOMODULATORS	381
SYNTHETIC IMMUNOMODULATORS (SI)	383
Bacillus Calmette-Guerin (BCG)	383
Muramyl Dipeptide (MDP)	383
Lipopolysaccharide (LPS) [42]	383
Levamisole	384
Isoprenosine	384
Pyrimidine Derivatives [46]	384
Purine Derivatives [47]	384
Nitrogen Mustard Alkylating Agents [48]	385
Synthetic Corticosteroids [49]	385
Heterocyclic Structures	385
Aromatic Compounds	385

Simple Non-cyclic Chemicals	385
MECHANISM OF SYNTHETIC IMMUNOMODULATORS	385
MARKET ANALYSIS [54-56]	386
SIGNIFICANCE OF NATURAL IMMUNOMODULATORS AND SYNTHETIC IMMUNOMODULATORS	386
Role of Immunomodulators in Human Health and Animal Health	386
COMPARATIVE SIDE EFFECTS OF IMMUNOMODULATORS CONSIDERING THEIR NATURAL & SYNTHETIC ORIGIN [61]	387
INDUSTRIAL MANUFACTURERS [62, 63]	388
CONCLUSION	388
CONSENT FOR PUBLICATION	389
CONFLICT OF INTEREST	389
ACKNOWLEDGEMENTS	389
REFERENCES	389
CHAPTER 12 FUTURE PATH AND PERSPECTIVES OF IMMUNOMODULATORS	399
<i>Megha Karne, Supriya G. Jagtap, Sujata Sawarkar and Vandana S. Nikam</i>	
INTRODUCTION	399
THE COMPLEXITY OF INNATE AND ADAPTIVE IMMUNITY	400
Approaches and Challenges in Standardization of Natural Immunomodulators	401
<i>In-vitro, In-vivo</i> Preclinical Models Development and Translating for Clinical Application	405
Novel Drug Delivery System of Natural Immunomodulators and Challenges, Future Outlook	406
Market and Regulatory Perspective of Natural Immunomodulators	408
CONCLUDING REMARKS	409
CONSENT FOR PUBLICATION	410
CONFLICT OF INTEREST	410
ACKNOWLEDGEMENTS	410
REFERENCES	410
SUBJECT INDEX	413

PREFACE 1

Immunomodulatory drugs, of both natural and synthetic origin, are increasingly being researched & developed for the treatment of human diseases, together with inflammatory disorders. In the post-SARS-CoV-2 pandemic of 2020, the research in immunomodulators has been found to be increased. The significance of such compounds, which focus on modulation of our immune status over remedial drugs, has been realized. Regardless of its extraordinary efficiency and specificity, the distortion of immune responses can be accountable for several disorders, such as autoimmune diseases, allergies, immunosuppression, and AIDS. Immunomodulators play a key role in diming such disorders too. In the past ten years (2011 to 2021), there have been several hundred reviews either on immunomodulators or combined with vaccines and adjuvants. However, a comprehensive book exclusively on all aspects of immunomodulators was needed for the clinicians, researchers, and Pharma & Biopharma professionals. Eminent and well-experienced professors, researchers, bioscience industry professionals, and technologists from India congregate to review this in the form of a comprehensive book. The book with the title “Natural Immunomodulators: promising therapy for disease management” encompasses all aspects such as ways of modulating immunity, diseases & disorders related to immunity, natural & synthetic immunomodulators, related analytical techniques, bioassays, and other methods for immunomodulators in the preclinical and clinical setting, delivery of immunomodulators: challenges and novel approaches, marketing strategy and regulatory perspectives, future path, and perspectives, *etc.* A glance through the twelve chapters reveals the vastness of the work on immunomodulators and their significance for mankind. The content of the book is like a crisp encyclopedia on the topic. The distinguished editorial team has refined the content to make it a ready one-stop reference for researchers, investors, bioscience & biotech professionals, vaccine developers, students, clinicians, *etc.* All the authors with decades of proficiency in the medical and clinical field put all their best effort to encompass the key literature in the past two decades along with representative historical aspects. I look upon this book as a high-impact reference.

Girish B. Mahajan
Senior Vice-President,
HiMedia Laboratories Pvt Ltd.,
Maharashtra, India

PREFACE 2

With the advancement and rapidly changing technology, information is accumulating in ever intimidating quantities with facts and figures that give logical reasoning, simple explanations about chaotic mechanisms, and the complexity of biology and life. Scientific knowledge is full of paradoxes, and with the addition of new information, it becomes easy and simple to unravel the unknown to known with rational justification.

Our book, entitled Natural Immunomodulators: promising therapy for disease management, is a small effort to gather recent updates in the field of immunology, pathology, and immunomodulatory therapies intended at harnessing the power of nature. Although the information is ever expanding in volume, we have taken intense efforts to conceptualize and summarize the information that emphasizes the significance of natural immunomodulators.

The immune system complexity is secondary to the nervous and endocrine systems. The immune system has a profound impact and involvement in emerging lifestyle-related chronic illnesses and infectious diseases. The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the year 2019 had underscored the significance of immunity. Moreover, the recent discovery of the brain lymphatic system in 2015 had stated the linkages of the immune system in neuropathology.

Our book provides a preview of the immune system and every aspect of natural immunomodulators, including their natural sources, standardization, novel drug delivery methods, marketing, regulatory requirements, challenges, and limitations to get them in mainstream in line with and parallel to modern medicines. The retrieved scientific information from literature is presented comprehensively without losing the essence of the research to readers, and the content is abstracted succinctly in simple, lucid language.

The successful completion of our book was possible due to the collective efforts and support from chapter authors, our research students, friends, and colleagues. We thank all of them for their sincere contributions in shaping this book. Finally, we are also grateful to the Bentham publishing team for their outstanding support and cooperation.

Vandana S. Nikam
Department of Pharmacology
STESS' Smt. Kashibai Navale College of Pharmacy
S. P. Pune University
Pune 411048 Maharashtra
India

List of Contributors

Ankita Dudhal	Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
Aishwarya R. Nale	Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune, Maharashtra, India
Akalya Sendrayakannan	Department of Food Engineering and Technology, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology (ICT), Nathalal Parekha Marg, Matunga, Mumbai 400 019, India
Abhijeet S. Kate	Department of Natural Products, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India
Aaliya Liyakath Ali	Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India
Alveera Ansari	Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India
Chaitrali Shevkar	Department of Natural Products, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India
Gaurav Doshi	Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India
Girish B Mahajan	HiMedia Laboratories Pvt Ltd, Maharashtra, India
Lakshmi Balachandran	Freelance Medical Writer, Maharashtra, India
Manali S. Dalvi	Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
Monika Kale	Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
Mukta Abhyankar	Department of Pharmacognosy, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
Mansi Damani	Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, University of Mumbai, India
Megha Karne	Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune, Maharashtra, India
Nikhil Putta	Department of Pharmacognosy, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
Namrata Nailwal	Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India
Pooja Shimpi	1Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune, Maharashtra, India
Prashant S. Kharkar	Department of Food Engineering and Technology, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology (ICT), Nathalal Parekha Marg, Matunga, Mumbai 400 019, India
Priyanka P. Nigade	Department of Pharmacology, STES's Smt. Kashibai Navale college of Pharmacy, Kondhwa, S.P. Pune University, Pune, Maharashtra, India

iv

- Pranjali S. Dhamane** M. Pharm Pharmacology, STES's, Smt. Kashibai Navale College of Pharmacy, Kondhwa (Bk), Pune-411048, Maharashtra, India
- Prabha Singh** Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, University of Mumbai, India
- Sanjay D. Sawant** Department of Pharmaceutical Chemistry, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
- Smita Pillewan** D.Y. Patil College of Pharmacy, Akurdi, S.P. Pune University, Pune, Maharashtra, India
- Supriya Jagtap** Department of Pharmacognosy, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
- Sujata Sawarkar** Department of Pharmaceutics, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India
- Vandana S. Nikam** Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India
- Vishal Bhange** Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune 411048, Maharashtra, India

CHAPTER 1**Introduction: Immune System & Modulation of Immune System****Manali S. Dalvi¹, Sanjay D. Sawant² and Vandana S. Nikam^{1,*}**

¹ Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune 411048, Maharashtra, India

² Department of Pharmaceutical Chemistry, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune 411048, Maharashtra, India

Abstract: The immune system is a complex, intricate organ system with features like flexibility, recognition, discriminating potential between self from non-self, and memory to defeat notorious external and internal threats to human health functioning. Innate immunity is inborn, and acquired immunity develops through secondary education; they are interconnected, interdependent, and execute tasks with bi-directional communications. A deeper understanding of immune biology revealed a remarkable contribution of the immune system in several chronic illnesses, and has taken a central stage in pathophysiology. In essence, the weakened or overactivated immune system leads to these chronic illnesses. Modulation of the immune system is an efficient and valid approach to prevent the underlying pathophysiology of such diseases. A gamut of natural immunomodulators targeted at specific or non-specific immune cells has delineated their potential to achieve the equilibrated and balanced immune system. Preclinical and clinical studies demonstrated the implication of microbiota, nutrients, natural herbs, and micronutrients for immunostasis. The immune system's complexity, its close association with the endocrine and nervous system, target identification, and convenient, reliable tools to assess immune function and modulation are a few limitations that hampered the attainment of immunostasis. Despite these limitations, novel therapies targeted at immunomodulation in chronic diseases are promising and paving the future path to novel therapeutics.

Keywords: Adaptive Immunity, Immune System, Innate Immunity, Immunomodulation.

INTRODUCTION

The principal components of the immune system are innate and adaptive immunity. The immune system is an older system on the evolutionary scale, and among

* Corresponding author **Vandana S. Nikam:** Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune 411048, Maharashtra, India; Tel: +912026931322; E-mail: nikam_vandana@yahoo.com

the two, the innate immune system is the ancestral one, present in both invertebrates and vertebrates [1]. The innate system is considered as the first line of defense for invading infection, growing neoplastic cells, or any other foreign matter in the body. The innate system lacks clonal expansion, memory, and antibodies and does not respond to changes in external stimuli. The innate system reacts and responds through its receptors to highly conserved microbial proteins like lipoteichoic acids and lipopolysaccharide of gram-negative and gram-positive bacteria, respectively [2, 3].

Immunity is the mechanism by which the body protects itself against diverse environmental agents, such as microorganisms or their product lines, food, chemical products, drugs, and pollen grains. The word 'Immunity' originated from the Latin word 'Immunis', which means 'exempt from public services' (from im-, in- not, un-, without+munus duty, task, service). The very first term was introduced in B.C. 430 during the plague of Athens. Thucydides noticed that people who had managed to recover from a prior bout of the disease were capable of treating the sick without becoming sick on the second contact [4]. Later Rhazes (880-932) termed the immunity as acquired immunity with an explanation of excess moisture being expelled from the blood and therefore preventing the subsequent occurrence of the disease. This theory explains the term acquired immunity as smallpox bout was effective in protecting its survivors from future infections and explains several terms about smallpox known during the 10th century. Louis Pasteur reconfirmed these observations in his germ theory of disease [5], which were later proven by Robert Koch in 1891 and awarded with Nobel prize. In the 19th century, Paul Ehrlich had a substantial contribution to immunology by proposing the side-chain theory, explaining the specificity of the antigen-antibody reaction.

The immune system can be defined as the bodily system that produces the immune response to protect the body from foreign materials, cells, and tissues. It is the body's defense mechanism to render foreign antigens and disease-causing bacteria from entering the body. It never attacks commensal flora that inhabits the gut, skin, and other tissues to the host's benefit and always differentiates between individual own cells and other harmful invading cells. All animals have nearly the same immune system, but it varies within individuals. It varies as a consequence of heritable and non-heritable influences [6].

COMPONENTS OF THE IMMUNE SYSTEM

Immune system differs from other systems in the body, as the cells involved in the system are highly motile. It specifically uses the blood vessels and lymphatic vessels to reach the infection site in order to move in and out of the lymphatic tissue.

Though the immune system is found all over the body, it still contains some specialized organs, which regulate the immune response and are capable of rapidly producing numerous cells that can stop spreading infection. Immune cells present in the reservoir can penetrate any cells in the body to combat the invasion. All the cells in the body originate from hematopoietic stem cells in the bone marrow as a precursor, but their site of origin and residence differ from each other [7]. The thymus and bone marrow are primary immune organs. Secondary immune organs include the lymph nodes, spleen, Peyer's patches, appendix, tonsil, adenoids and other mucosal-associated lymphoid tissue (MALT) [8] Fig.(1).

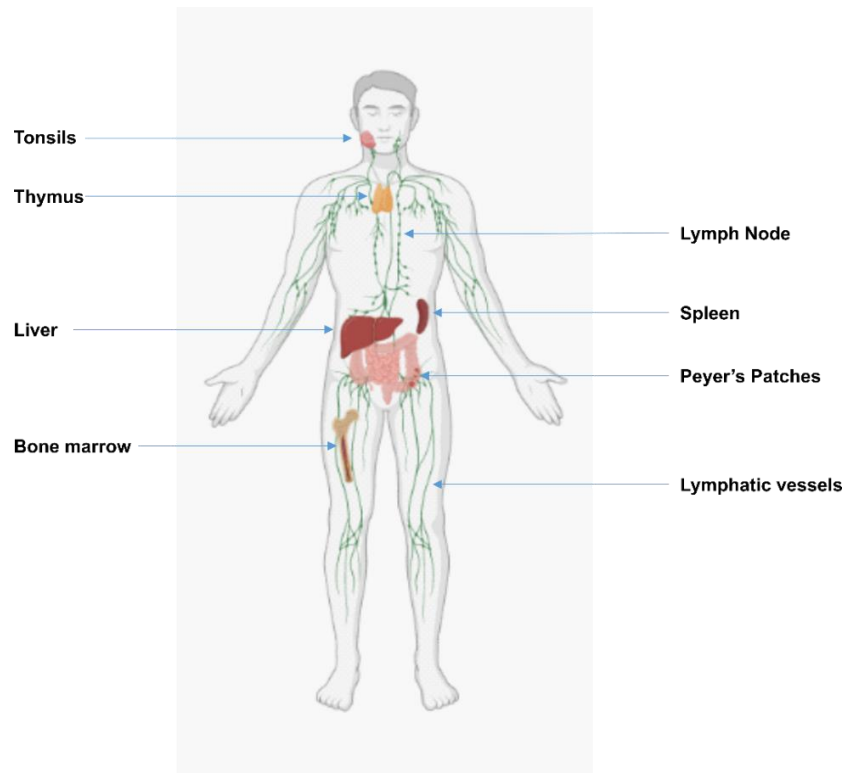


Fig. (1). Primary and secondary immune organs of human body.

Bone Marrow

It is the primary site for blood cell synthesis. It gives rise to all types of precursor blood cells. Red bone marrow is a connective tissue that is highly vascularized, having 0.05 to 0.1% pluripotent stem cells derived from mesenchyme. These cells proliferate; differentiate into lymphoid and myeloid stem cells, which give rise to lymphocytes and myeloid cells, respectively. These stem cells further differentiate and become committed progenitor cells, which give rise to specific blood cell types. Some progenitor cells are also referred to as colony-forming units (CFU)

CHAPTER 2**Diseases and Disorders Associated with Immune System****Pooja Shimpi¹, Smita Pillewan² and Vandana S. Nikam^{1*}**¹ *Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India*² *D.Y. Patil College of Pharmacy, Akurdi, S. P. Pune University, Pune, Maharashtra, India*

Abstract: The human immune system is one of the complex systems of the body, which works against both external and internal invasion. It has two parts: the innate and the acquired immune systems. We have been born with the innate system which gives a quick response for the invading pathogen non-specifically. To deal with the typical environmental antigens, immune system adapts to changes. The acquired (or adaptive) component develops over time and produces antibodies that “remember” invaders to fight them if they return. Failure of it could be due to genetic defect (weak natural immunity), inability to adapt to the change, hyper-responsiveness, or inability to distinguish self from foreign, leading to various diseases and disorders. Various genetic defects of the immune system are at the core of Primary Immune disorders (PIDs), while overactivity is responsible for allergic diseases. Autoimmune diseases are mostly due to malfunction of the adaptive immune system, while in Systemic Auto-inflammatory Disorders (SAIDs), the innate immune system is affected. Advancements in technology and genetics have improved our understanding of the pathogenesis, diagnosis, and management of these diseases.

Keywords: Autoimmunity, Allergic Diseases, Auto-inflammation, Cancer Immunotherapy, Immunological Disorders, Immunodeficiency, Neuro-immune System.

INTRODUCTION

The immune system is an efficient complex network of cellular elements, molecules, and pathways that is evolved to protect the host or multicellular organisms against external offends or invaders, and its balance functioning is essential to avoid the development of various disorders. In a normal infectious state, the infectious agent activates the innate immune response, which causes symptoms followed by an adaptive immune response that leads to clear infections

* **Corresponding author Vandana S. Nikam:** Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India; E-mail: nikam_vandana@yahoo.com

and develops a protective immunity state. But in several circumstances, this will not happen, and there can be a failure of the host Immune response against the invasive agents. The failure of the host immune system can be due to avoidance of a normal immune response by pathogens; genetic defects give rise to failures of defence mechanisms, immunodeficiency syndromes, autoimmunity, allergic responses, *etc.* The prevalence of Immune disorders is on the rise, as many new rare disorders have been identified in the last few decades. Autoimmune Diseases (ADs) account for about 3–5% of the world population, whereas a 30 to 40% rise in allergic disorders is seen. Major advancements in technology and genetics have improved our understanding of the pathogenesis, diagnosis, and management of these diseases [1 - 3].

CLASSIFICATION OF IMMUNE DISEASES AND DISORDERS

When we talk about immunological diseases and immunological disorders, we can sketch a marked line between these two terms. The term immunological disease is ascribed to the situation in which the part, organ, or organ systems of the body get affected by various internal or external factors, whereas immunological disorders are characterized by irregularity or failure of organ function or organ system. The immunological disorders can be physical, structural, genetic, and behavioural. The immune diseases and disorders can be classified based on Organ-specific and organ-non-specific, or we can classify them as Phenotypic diseases or disorders according to the Inborn Errors of Immunity Committee (IEIC). The immune system works for the protection of the body.

BROAD CLASSIFICATION OF IMMUNE DISEASES AND DISORDERS

- I. Immunodeficiency disorders
- II. Allergic/ Hypersensitivity reactions
- III. Autoimmune disorders
- IV. Auto-inflammatory disorders

Immunodeficiencies (IDs)

A person with immune deficiency syndromes has lost the ability of one or more components of the immune system to respond protectively to a pathogen. Immunodeficiencies (IDs) are a group of diseases with alterations in either inborn or adaptive immune responses. They are classified as primary when of genetic origin, more recently called inborn errors of immunity (IEI), and secondary when they are acquired [4]. Primary immunodeficiencies (PIDs) include approximately 420 monogenic diseases that are more susceptible to infections and non-infectious complications, including allergies, malignancies and autoimmune diseases (ADs),

which also include developmental disorders, autism, intellectual disability, epilepsy, gastroenteropathies, pneumopathies, dermatoses, skeletal and renal abnormalities [5]. There are two types of PIDS. Monogenic immunodeficiencies occur because of mutations in genes responsible for immunological tolerance, thus triggering autoimmunity, including poly-autoimmunity and polygenic immunodeficiencies with a complex pathophysiology and having a multifactorial etiology.

Classification of Immune Diseases and Disorders Based on Inborn Errors of Immunity

Inborn errors of immunity are also known as primary Immunodeficiencies. All types of inborn errors of immunity are compiled by the International Union of Immunological Societies Expert Committee. The important manifestations of primary immunodeficiency are the increased sensitivity to auto-inflammatory diseases, autoimmunity, and allergic diseases. According to the ISEC committee, primary Immunodeficiencies can be classified into 10 classes Table 1.

Table 1. Classification of immunodeficiency disorders.

Immunodeficiency Disorders		
Class	Subclass	Disease/Disorder
<i>Immunodeficiencies Affecting Cellular and Humoral Immunity</i>	T-B+ severe combined immune deficiency (SCID)	i. CD45 deficiency ii. L7R α deficiency iii. AK3 deficiency iv. Coronin-1A deficiency
	T-B- SCID	i. RAG deficiency ii. AK2 defect iii. DCLRE1C (Artemis) deficiency iv. DNA ligase IV deficiency v. Adenosine deaminase (ADA) deficiency
	Combined immunodeficiency (CID), generally less profound than SCID	i. CD40 ligand (CD154) deficiency ii. CD40 deficiency iii. D3 γ deficiency iv. ICOS deficiency

CHAPTER 3**Natural Sources of Immunomodulators****Vishal Bhange¹, Monika Kale¹, Ankita Dudhal¹, Nikhil Putta², Mukta Abhyankar², Supriya Jagtap² and Vandana S. Nikam^{1,*}**¹ Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune 411048, Maharashtra, India² Department of Pharmacognosy, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune 411048, Maharashtra, India

Abstract: Nature is replete with an arsenal of compounds that can be investigated for their therapeutic potential. The immune system involvement in severe chronic illnesses or emerging infectious diseases has provided clinical evidence. The prevention and treatment of these diseases targeted at the immune system with natural immunomodulators are gaining momentum, owing to their diverse array of activities. Treating acute illnesses with modern medicines has been successful; however, treating chronic illness treatment remains elusive and disappointing. Notably, this chapter reviews the natural resources of immunomodulators. Natural immunomodulators from plants, marine, and animals are of prime importance, and they possess many pharmacological activities. Similarly, microbiota modifiers - prebiotics, probiotics, and micronutrients- are imperative in restoring immune homeostasis. This chapter summarizes these natural immunomodulators and their power to boost immunity and human well-being.

Keywords: Alkaloids, Glycosides, Micronutrients, Microbiota, Natural Immunomodulators, Prebiotics, Probiotics.

INTRODUCTION

Immunopharmacology, the most upcoming and rapidly developing branch of pharmacology, deals with pharmacology, immunology and pathology. It holds considerable potential for the prophylaxis and treatment of various spectrum of immune system illnesses and disorders. The etiology and pathophysiology of many diseases are known to be influenced by the host's immune system's specific and non-specific defences. Almost every culture has a history of herbalism, depending on the natural flora and vegetation and evidence of harnessing the power of natural remedies to heal human diseases and disorders. Ayurveda (Ayu:

* **Corresponding author Vandana S. Nikam:** Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune 411048, Maharashtra, India; Tel: +9130806361; E-mail: vandananikam@sinhgad.edu

(Ayu: Life Veda: Knowledge), 'the science of life, is the world's oldest system of medicine and has enlisted various indigenous herbal and herbo-mineral formulations (for example, Shilajit) for human well-being.

Regulation of immune response to alleviate illnesses has piqued interest for many years, and the Ayurvedic notion of Rasayana is built on similar concepts. Many factors, such as medications and stress hormones, can affect the immune system's function and efficiency, resulting in either immunostimulation or immunosuppression. The healthy state is thought to be the result of a complex fine-tuning of immunoregulatory mechanisms. Immunomodulators are agents that maintain the homeostasis of the host immune system either by immunostimulation or by immunosuppression.

In light of the current context where the emergence of viral diseases like AIDS, hepatitis, and Severe Acute Respiratory Syndrome CoronaVirus (SARS-CoV) are viewed, and host defenses are compromised, the concept of Rasayana in Ayurveda as we understand, it seems to be imperative as it elevates the host defenses. Immunomodulatory medications may be used in clinical settings to restore immunological insufficiency, as in AIDS and other viral diseases, or to reduce normal or excessive immune efficiency, as in transplant rejection and autoimmune disorders.

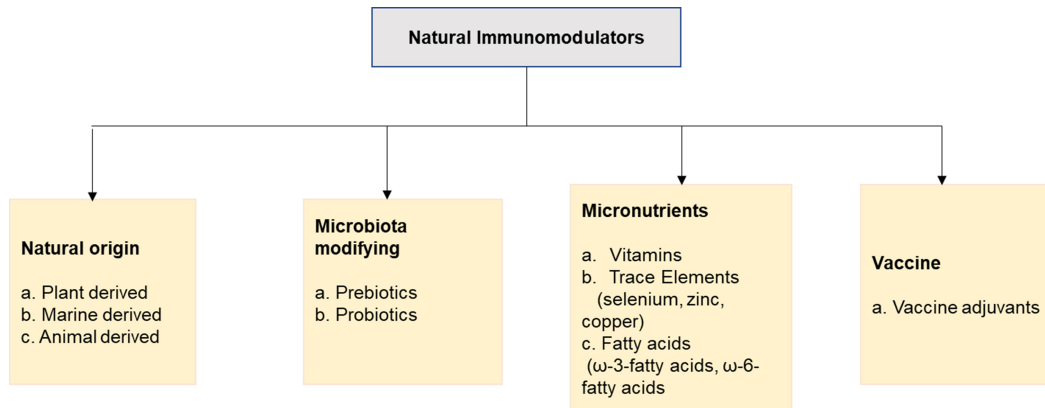


Fig. (1). Classification of natural immunomodulators.

The literature is replete with a plethora of natural immunomodulators derived from several sources like plants, animals and marines. The cross-talk between immune cells and natural microbial flora also has a significant role in immunity, and disturbed immune function can be corrected with the use of microbiota-modifying reagents like prebiotics and probiotics. Based on their sources and role,

natural immunomodulators are broadly classified into many groups, as depicted in Fig. (1) [1 - 4].

PLANTS AS SOURCE OF IMMUNOMODULATORS

Herbal medicine is one of the most ancient forms of remedial treatment evolving with humanity. A retrospection of the healing power of plants and a return to natural remedies is an absolute need of our times. Herbal medicine is based upon the principles that plants contain. As research on herbals continues, an increasing number of plants is becoming recognized as immunomodulators. Table 1 and Fig. (2).

Glycosides

These organic compounds from plant sources are degraded by enzymes, yielding one or even more glucose molecules. They are acetals, or sugar elixirs, which are formed when the hydroxy groups of glucose and non-sugar molecules come in contact with the loss of a hydroxyl group. A number of glycosides have been shown to have immunomodulatory properties. *Picrorhiza scrophulariiflora* iridoid glycosides [1] and *Andrographis paniculata* anthraquinone glycosides [2] are two examples of them. Dendroside A and dendronobilosides A and B, three novel sesquiterpene glycosides, have been identified in the stem of *Dendrobium nobile*, a plant used in traditional Chinese medicine. Dendroside A and dendronobilosides A were known to increase the proliferation of murine T and B lymphocytes *in vitro*, although dendronobiloside B inhibited it [5].

These are some of the widely spread organic compounds in plants, present as free-state glycosides. They are mostly made up of water-soluble chemicals. The carbon skeleton of their molecular structure is C6-C3-C6. Flavonoids are powerful water-soluble strong antioxidants as well as free radical scavengers that protect cells from oxidative damage. They also have great anti-cancer properties, which protect against all phases of carcinogens. Flavonoids in the blood have been related to a decreased risk of heart disease [5]. They impede the initiation, propagation, and advancement of malignancies in terms of anti-cancer action. Plant flavonoids, with chemoprotective agents, have recently garnered the attention of many researchers as a highly essential dietary supplement for people with cancer [6, 7].

Tannins

Tannins are amorphous, seldom crystalline compounds that are astringent and bitter in taste. They are soluble in water and alcohol. They are phenolic compounds, classified chemically based on the hydrolysis product.

Standardization of Immunomodulator Natural Drugs

Aishwarya R. Nale¹ and Supriya G. Jagtap^{2,*}

¹ Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S.P. Pune University, Pune, Maharashtra, India

² Department of Pharmacognosy, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India

Abstract: Natural medications are gaining popularity as people become more aware of their benefits and accept their use in modern medicine. Natural drugs have demonstrated extensive suitability as curative agents for various disorders due to their fewer side effects and toxicity. Scientists face a tremendous problem in developing accurate analytical techniques that can efficiently profile the contents of phytochemicals. This is in addition to quantitative studies of marker or bioactive chemicals and some other important ingredients. Natural medicines, on the other hand, lack standardized parameters. Standardization is a vital step towards the formation of a constant chemical profile, consistent biological activity, or just a quality assurance programme for the production and manufacturing of natural products. As a requirement for global harmonization, the WHO criteria for assessing the safety, efficacy, and quality of natural drugs are extremely important. Scientific research of some of the natural origin plants regarded in Ayurvedic Rasayana for their beneficial potential has generated good results. The number of plants with a potential immunomodulatory activity that has been cultivated using conventional or cell culture methods is standardized. This can help to portray and validate their usage in folk medicine in the early days, as well as give an establishment for future investigation. The goal of this chapter is to showcase the findings of research evidence on standardized natural plant-origin immunomodulators. The chapter also goes through biological screening strategies for diverse plant medications with the goal of revealing the immunomodulation mechanism. Researchers will hopefully be encouraged to pursue more research on medicinal plants with immunomodulatory potential as a result of this study.

Keywords: Immunomodulators, Immunostimulants, Immunosuppressants, Natural Drugs, Plant Tissue Culture, Standardization.

* Corresponding author Supriya G. Jagtap: Department of Pharmacognosy, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India; Tel:+918888837747; E-mail: supriyashinde2003@gmail.com

INTRODUCTION

Natural drugs are the use of plants and plant remedies in the prevention and control of diseases. Plants have been utilized medicinally by societies all over the globe for more than thousands of years and contains a primary resource of drugs throughout human history. The fact that they are still extensively used nowadays is not a relic of the Dark Ages, but rather a sign that natural-origins plants are becoming an element of current high-tech medicine. Natural drugs act as an imperative role in the scientific structures of a few countries, like Ayurvedic medicine in India and Traditional Chinese Medicine (TCM), which, along with various complementary therapies, are seeing renewed interest. Natural drugs are recognized by the WHO as an essential component of primary health care and are 3 to 4 times more widely used than traditional medicine worldwide. According to the WHO, traditional medicine is used by 65–80% of the worldwide population as a primary resource of healthcare, and 40% of the worldwide population relies directly on traditional medicine for healthcare (WHO, 2003). It has also been discovered that nearly 15,000 plant species out of 45,000 are used for their precise medicinal value, demonstrating the significant diversity of plant species [1, 2].

According to the report, more than 130 compounds derived from approximately 100 plant species can be considered important drugs, with 77 percent presently utilized in one or more countries. Phytomedicines are flooding the markets of developed countries, and consumers all over the world have demonstrated a desire for natural drugs and their formulations. The emphasis is on ‘natural is better’ [3].

Today, Ayurveda has evolved into a scientific system of holistic healing that is now recognised all over the world [4].

Ayurveda is the Sanskrit word for “life science”. It is not merely a system of medicine, however, but a general philosophical technique for maintaining good health, living a long life, and treating diseases. It provides a sole blend of science and philosophy that balances the physical, emotional, mental, and spiritual components required for lasting health. This healing system believes in treating the entire person, not just the part affected by the disease. Furthermore, the emphasis is on prevention rather than cure [5].

Ayurveda evolved in tandem with religion and mythology. It can be thought of as a stream of knowledge that has been passed down from time immemorial and has been reinterpreted and brought along with it. Ayurveda is possibly the only organized science that directs ecological development, medicinal plant cultivation, and the use of specific plant parts [6].

More than 2000 drugs are listed in the “Charaka” and “Sushruta” samhitas, with 70% of them being herbal. The importance of this science will continue to grow due to its biomedical implications and place in cultural beliefs. Despite its ability to treat a wide range of diseases, medicinal plant therapy was developed in preindustrial times [6].

Besides Ayurveda, a variety of healthcare systems have been practised around the world, including Siddha, Unani, and Homeopathy, the majority of which are based primarily on herbs and diet. Globally, the early twentieth century saw a decline in the popularity of natural drugs of plant origin due to the evolution of the pharmaceutical industry (synthetic medicines), as well as a lack of interest in medicinal plant research [5].

However, the pendulum has recently dangled back, and there is a reappearance of awareness in the study and application of plant-based drugs. Natural drugs are in high demand, particularly those scientifically validated, such as Garlic, Echinacea, Ginseng *etc.* ‘Herbalism’ refers to the more recent perception of using herbs or plants in a more scientific way [7, 8]. Since the origin of civilization, plants and plant compounds have been utilized as natural drugs. They are used to care for a wide range of acute and chronic illnesses, from the common cold to complex human problems, and they're regarded as the cornerstone of indigenous drugs [9]. As per WHO opinion, approximately 80% of the worldwide population anticipates using natural products for health care owing to their fewer side effects and the high price of modern medicine [10].

As the environment becomes more polluted, life becomes more stressful, and food becomes contaminated by chemicals, there is a greater need to reconnect with nature. Although allopathy and modern medicine are unquestionably effective and necessary in certain situations, there are some pitfalls where an alternative system of medicine offers some advantages.

NEED FOR DRUGS FROM PLANT ORIGINS OVER SYNTHETIC DRUGS

Allopathic treatment entails the administration of drugs that introduce toxins into the body. The body may be unable to eliminate or cope with them, resulting in adverse effects. Herbal medicines, which are based on a traditional system of natural cure, cleanse the body, increasing its ability to heal itself and defend against invaders while causing virtually no side effects.

Allopathic treatments are incapable of providing long-term solutions. Its most prevalent strategy is to suppress both physical and mental signs and symptoms. Natural drugs treat the symptoms as an indication or evidence of a deeper

CHAPTER 5

Immunomodulators: Chemistry and Analytical Techniques

Akalya Sendrayakannan¹ and Prashant S. Kharkar^{1,*}

¹ Department of Food Engineering and Technology, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology (ICT), Nathalal Parekha Marg, Matunga, Mumbai 400 019, India

Abstract: Immunomodulators are substances that either enhance or suppress the immunity of the host. Immunomodulators have been used for ages in Ayurvedic Medicine and Traditional Chinese Medicine. In the surge of modern medicine, many chemically derived substances are used as immunomodulators. Historically, plants present a rich source of these therapeutic agents. Researchers have used these lead structures for exploring the underlying mechanisms of immunomodulation so that newer, safer agents can be designed and used clinically. Microbial sources have also been tried in search of immunomodulators. Chemically, these are a diverse group of substances that act on varied signaling pathways to cause immunomodulation. The involvement of the immune system in many diseases and disorders makes these agents essential in the treatment of these diseases, *e.g.*, cancer. This chapter discusses the chemistry of a selected few commonly known plant-derived immunomodulators along with their biological evaluation methods and provides a broad overview of their therapeutic potential with particular emphasis on the mechanism of immunomodulation.

Keywords: Adaptive Immunity, Cytokines, Emodin, Immune checkpoint inhibitors, Immunomodulators, Innate Immunity, Interleukins, Quercetin.

INTRODUCTION

Innate immunity is the first line of defense that is present in almost all vertebrates and even in the multicellular organisms; its main role being recognition of the foreign invaders such as pathogens. In most cases, the innate immune system recognizes a particular region of the pathogen known as Pathogen Associated Molecular Patterns (PAMPs) employing the so-called Pathogen Associated Receptors (PARs). The other arm of the immune system, *i.e.*, adaptive immunity,

* Corresponding author Prashant S. Kharkar: Department of Food Engineering and Technology, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology (ICT), Nathalal Parekha Marg, Matunga, Mumbai 400 019, India, E-mail: ps.kharkar@ictmumbai.edu.in

involves the generation of B and T cell receptors somatically during the B and T cell development and so are not passed on to the next generation. Hence antigenic determination cannot be made by them until they are being made to recognize them [1]. In other words, the innate immune system is more general in its capability to identify the antigens, whereas the adaptive immune system is more specific in this aspect.

The innate immune system comprises of cells such as mast cells, basophils, natural killer (NK) cells, macrophages, eosinophils, neutrophils, and dendritic cells. These cells have their way of killing and eliminating the pathogens, some of which include releasing histamines, cytokines, or chemokines, or making the cells follow the apoptotic (programmed cell death) path, by phagocytosis, or presenting the antigens to T cells. The adaptive immune system comprises of B cells, CD4+, and CD8+ cells. The B cells eliminate the pathogen mostly by the humoral immune response or by producing antibodies. The CD8+ cells recognize most of the cancerous and virus-infected cells (intracellular pathogens) and make them undergo apoptotic pathways. The CD4+ cells, which constitute Th1, Th2, Th17, and regulatory T (Treg) cells, are involved in the production of cytokines such as Interferon γ (IFN- γ), Interleukin-2 (IL-2), IL-4, IL-5, IL-13 and IL-17 [2].

The immune system is capable of recognizing self (own body cells, proteins), from non-self (antigen), which could be anything such as the viral coat, bacterial lipopolysaccharides, viral genetic material, or any substance which does not belong to the host. The problem arises if the immune system does not recognize particular antigens resulting in a particular disease (or pathological condition) or if it recognizes its own body cells that result in auto-immune disease or disorder. The latter is mostly because of the adaptive immune response since the antigen-binding site is a result of a random genetic mechanism [1]. The role of immunomodulators is essential in these cases, which helps to maintain the homeostasis of the immune system. The present chapter thoroughly discusses the chemistry of various immunomodulators derived from natural sources, followed by the analytical techniques and finally, the efficacy of immune modulation demonstrated by some of the plant-derived immunomodulators.

IMMUNOMODULATORS

Precisely, immunomodulators are substances that help to maintain the homeostasis of the immune system, *i.e.*, it could be either immunosuppressant or immunostimulant or immunoadjuvant. These agents are administered to maintain the balanced functioning of the immune system. The immunosuppressants are agents that aid in suppressing the immune system. The suppressed immune function is desirable in patients suffering from auto-immune diseases such as

rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), or for suppressing the immune response in patients who have undergone organ transplant surgery to prevent graft rejection [2]. On the other hand, the immunostimulants are agents which enhance or boost the immunity of the host. Immunostimulants are mostly indicated for providing resistance to some diseases, leading to enhanced immunity without the use of vaccines [3], *e.g.*, various Immunostimulants prescribed during the COVID-19 pandemic. The immunoadjuvants are those substances which are used in a vaccine along with the antigens as carrier material. The antigen itself, in this case, would be very small and hence will not be recognizable by the host immune response. So, immunoadjuvants are used, which aid in better recognition by the immune system, leading to the profuse response by the immune system and hence, improved protection [4]. Both the Immunostimulants and immunomodulators may work *via* specific pathways or non-specifically. With respect to chemotypes, the immunomodulators could be small-molecules, proteins or peptides, carbohydrates, nucleic acids, or lipids [5]. While the field of immunomodulators is so very vast, no attempt is made to discuss all the types of immunomodulators but small-molecules, particularly those obtained from natural sources.

Commercially, many immunosuppressants are available, some of which include Rapamycin (1), Sirolimus, Fig. (1) Cyclosporin A (2), Cyclophosphamide (3), Azathioprine (4), and Cinanserine (5). Rapamycin, a macrocyclic compound produced by *Streptomyces hygroscopicus*, disrupts the T-cell growth-promoting cytokines like IL-2 or IL-4 and acts as an anti-proliferative agent. It blocks the cell cycle during the mid-to-late G1 phase, thereby arresting the G/S transition [6]. Cyclosporin A inhibits the action of calcineurin, which in turn blocks the movement of cytosolic components of the Nuclear Factor of Activated T-cell (NF-AT). Cyclophosphamide is the most widely used alkylating agent, which inhibits both the adaptive and innate immune responses. Azathioprine is an immunosuppressant that is generally used in kidney transplants, and Cinanserine is an antagonist of serotonin, which suppresses the antibodies circulating in the human body [3].

The synthetic drugs, though efficacious, come with debilitating adverse effects, including toxicity such as nephrotoxicity, neurotoxicity, and gastrointestinal toxicity, among others. Also, they act upon actively growing cells such as bone marrow cells which ultimately end up in leucopenia and thrombocytopenia [3]. Compared to synthetic drugs, natural products offer several advantages [7] due to the synergistic actions of complex molecules when used in the form of an extract or preparation. At times, pure natural products offer distinct pharmacological and therapeutic activities. The successful use of natural products as sources of new drugs has created enough research interest in the global scientific community [8].

CHAPTER 6

Bioassays and Other Methods for Immunomodulators in Preclinical and Clinical Setting

Priyanka P. Nigade¹, Pranjali S. Dhamane² and Vandana S. Nikam^{1,*}

¹ Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India

² M. Pharm Pharmacology, STES's, Smt. Kashibai Navale College of Pharmacy, Kondhwa (Bk), Pune-411048, Maharashtra, India

Abstract: The availability of appropriate animal models is essential for effective translation of immunomodulatory research into clinical settings. Bioassays and other methods for immunomodulators in the preclinical and clinical setting are being used to assess the quality and quantification of the immune response, find the best suitable route of administration and formulation method, protect the transmission of infection, and assess the safety and toxicity of immunomodulators. Identifying the appropriate animal model has become very important, since each model has its own pro's and cons. The scope of this chapter is to outline the assaying of immunomodulatory activity, the approaches and the experimental strategies. This chapter discusses various *in-vitro* models such as cell lines, assays and murine models, which are being used for quantification of the immune response, assessment of overall immune functions, immunosuppressive activity, screening of anti-allergic drugs and agents used in the treatment of various autoimmune disorders and transplant-related and autoimmune diseases. The most important questions that we should keep in mind while choosing a suitable animal model are, selection of suitable species, physiological relevance of model, immunological functions to be evaluated, and its practical implications.

Keywords: Adaptive Immunity, Immune System, Immunomodulation, Innate Immunity.

INTRODUCTION

Scientist Edward Jenner, who performed the first 'vaccination' against smallpox in 1796, brought the concept of Immunomodulation. Further, various efforts were undertaken to modify the immune system to combat both external and internal pathogen attacks, with the intention of improving disease resistance. With this

* Corresponding author Vandana S. Nikam: Department of Pharmacology, STES's Smt. Kashibai Navale college of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India; E-mail: vandananikam@sinhgad.edu

goal, the immune response can be modified by applying immunosuppression, immunostimulation, and immunorestitution [1 - 3]. Immuno-stimulatory adjuvants are required in vaccines to activate the innate immune system and generate specific adaptive immunological responses. Immunoadjuvants increase the amount of antibody generated while decreasing the amount of antigen required for injection and, as a result, the frequency of injection. Examples of best-known types of immunoadjuvants are Toll-like receptor agonists (TLR), inorganic immunoadjuvants, plant-derived immunoadjuvants, exosomes, and endogenous proteins. However, their short response rates and undesirable effects limit their use. As a result, there is a continued demand for immunoadjuvants with enhanced efficacy and lower toxicity, as well as improved bioactivity and bioavailability [4, 5]. Also, many novel multifunctional adjuvants are being developed with the modified delivery system. Nanoparticle-based immunoadjuvant [4] and the incorporation of multifunctional immunoadjuvants into pDNA/mRNA vaccines [6] are two of the most promising. Immunostimulants are appealing compounds that trigger the immune system for disease prevention and improve natural resistance to numerous viral and bacterial infections. Immunostimulants act in specific and non-specific ways in the body, causing the production of specific antibodies and cytokines, which can be used to treat infectious disorders and diseases with suppressed immunity like malignancies, AIDS, SARS, *etc* [7, 8]. Immunosuppressive drugs are used to treat severe hypersensitivity immune reactions, transplant-related and autoimmune diseases caused by autoreactive B lymphocytes or T lymphocytes (CD4+ or CD8+ cells) [9, 10].

ASSOCIATION OF INNATE IMMUNITY AND ADAPTIVE IMMUNITY AND THEIR MEASUREMENTS

Innate immunity is the first-line immune system with no memory generates fast and blunt, non-specific responses to infection and tissue injury in response to the signals from germline-coded proteins termed Pattern Recognition Receptors (PRRs). PRRs have evolved to recognize molecular patterns shared by numerous pathogen classes called Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs). To activate the adaptive immune system, dendritic cells, macrophages, mast cells, neutrophils, basophils and eosinophils directly interact with other cells or release cytokines and other compounds such as reactive oxygen species, nitric oxide, and lipid inflammatory mediators which are involved in the inflammatory response. Other lymphocytes without antigen specificity, such as gamma-delta T cells and Natural Killer (NK) cells, are considered innate cells with some resemblance to effector lymphocytes [11, 12]. Dendritic cells (DC) are important agents between innate and adaptive immunity by triggering primary immune responses. DC, as a component of the in-

nate immune system, organises and transports information from the outside world to the adaptive immune system [13].

Adaptive immunity generates an antigen-specific, flexible response and has immunologic memory. So, it permits vertebrates to thrive in an environment where they are constantly exposed to infections. This system relies on the clonal selection and expansion of lymphocytes *via* antigen (T cell and B cell) receptors. Antigen receptors are clonal receptors that have been genetically altered to bind to antigens expressed in Major Histocompatibility Complex (MHC) molecules on antigen-presenting cells [14].

Although the innate and adaptive immune systems are opposite, independent systems of the host response, they work together see Fig. (1). The innate system acts as the first line of defense against pathogens, thus activating antigen-specific cells. These antigen-specific cells further help in recognizing and responding to microorganisms. As a result, coordination between innate and adaptive immune responses is important, even though they operate *via* different mechanisms.

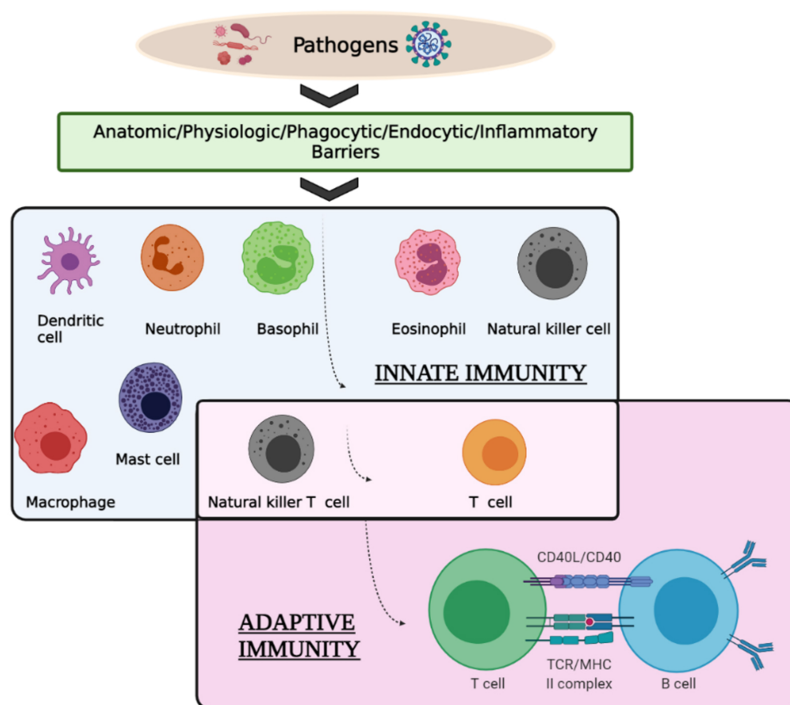


Fig. (1). Association between innate immunity and adaptive immunity.

Natural Immunomodulators in Cancer Therapy

Chaitrali Shevkar¹ and Abhijeet S. Kate^{1,*}

¹ Department of Natural Products, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, India

Abstract: Cancer is a complex disease, ranking among the top causes of mortality worldwide. There are numerous therapies available however, they are showing limited success in a complete cure. The advanced treatment regime includes immunotherapy that improves the body's natural defences. The approved immunotherapies are imiquimod (Zyclara[®]), lenalidomide (Revlimid[®]), pomalidomide (Pomalyst[®]), and thalidomide (Thalomid[®]). However, these therapies have severe side effects like nausea, high blood pressure, blood clot, severe allergies, *etc.* Hence, natural products with immunomodulatory properties are being widely used as adjuvant therapy in cancer treatment. Plant secondary metabolites, such as curcumin, resveratrol, zerumbone, quercetin, genistein and betulinic acid, which are used as a member of the cancer medications and possess immunomodulatory potential, have been described in this chapter. We have discussed the mode of action, *in vitro*, *in vivo*, formulation studies and plant source of these natural immunomodulators. This chapter also discusses the current state of these pure compounds in context to their development as anticancer treatments in the future.

Keywords: Anticancer, Antitumor, Curcumin, Cytotoxicity, Immunotherapy, Natural Immunomodulators, Quercetin and Betulinic Acid, Resveratrol.

INTRODUCTION

Cancer imposes the largest worldwide healthcare burden as it is the second prominent cause of death globally, accounting for approximately 9.6 million deaths in 2018 [1 - 3]. At present, chemotherapy, endocrine treatment, targeted cure, radiation, surgery and immunomodulation are used for the management of cancer [4]. Multiple genetic and epigenetic factors influence cancer cell sensitivity leading to drug resistance in cancer which has posed a huge challenge in cancer therapeutics [5]. High doses of a drug, rapid metabolism, higher elimination rate, lower bioavailability, adverse effects, and toxicity to normal cells are the drawbacks associated with the existing chemotherapeutics [6]. There are numero-

* Corresponding author Abhijeet S. Kate: Department of Natural Products, National Institute of Pharmaceutical Education and Research, Ahmedabad, Gujarat, 382355 India; E-mails: kate.abhi.s@gmail.com; abhijeetk@niprahm.ac.in

us adverse effects of radiation therapy as well like cardiovascular disease, dermatitis, pneumonitis, and sexual dysfunction [7]. Immunotherapy is a clinically validated emerging treatment for the management of broad cancer types [8]. Tumour's immune resistance mechanisms, such as specific immune responses mediating collateral tissue damage and immune-inhibitory pathways, can be effectively targeted against cancer [9].

The immunomodulatory checkpoints like cytotoxic T lymphocyte antigen 4, CD25+ (Interleukin-2 receptor alpha chain), CD4+ (cluster of differentiation 4), foxp3-expressing Tregs (suppressor T Cells), Interleukin-2 (IL-2) and Interleukin-15 (IL-15) are used as tools to enhance the effects of immunotherapeutic. Inhibiting pro-inflammatory cytokines like Interleukin-6 (IL-6), which activate the signal transducer and activator of transcription 3 (STAT3) and NF- κ B (nuclear factor kappa light chain enhancer of activated B cells) pathways, prevents the upregulation of anti-apoptotic peptides like Bcl-2 (B-cell lymphoma 2) [10, 11]. Macrophages infiltrating the tumour microenvironment prompt the immune response to counter the tumour by increasing reactive nitrogen and reactive oxygen species, leading to DNA impairment and tumour destruction [12]. Monoclonal antibodies in unmodified form or modified with add-on toxins and radionuclides are extensively used as magic bullets to treat cancer as an immunotherapeutic [13]. However, these monoclonal antibodies have limitations in cost, production and purification, risk of virus association, *etc* [14]. Currently, lenalidomide (Revlimid[®]), pomalidomide (Pomalyst[®]), Imiquimod (Zyclara[®]), and thalidomide (Thalomid[®]) are among the authorised immunotherapies against cancer. Lenalidomide and pomalidomide are the synthetic analogues of thalidomide used against several haematological malignancies and regulates various aspects of the immune system, including cytokine production, T cell co-stimulatory activity, and Natural Killer cell cytotoxicity [15, 16]. However, these therapies have severe side effects like severe allergies, nausea, high blood pressure and blood clot [17].

For ages, nature-based treatment systems, such as Ayurveda, Unani, Siddha, and Traditional Chinese Medicine have used immunomodulation for healing [18, 19]. Several plants like *Withania somnifera*, *Paris polyphylla*, *Astragalus melanophrurius*, *Astragalus oleifolius*, *Ocimum sanctum*, *Panax ginseng*, *Alternanthera tenella*, *Terminalia arjuna*, *Tinospora cordifolia*, *etc.* have been used as immunomodulatory agents [20]. These plants, in the form of various ayurvedic formulations such as Rasayanas, are known to inhibit tumour development in mice by improving natural killer (NK) cell activity while enhancing the production of Granulocyte-macrophage colony-stimulating factor (GM-CSF), Interferon gamma (INF- γ), and IL-2 [19]. A formulation of *Withania somnifera* containing a 1:1 ratio of alcoholic extract of roots and leaves showed

enhanced Type 1 T helper (Th1) expression in tumour-bearing mice, repressing the expression of STAT3. This formulation has also shown increased (cluster of differentiation 8) CD8⁺ and CD4⁺ T cell proliferation which is useful in inhibiting cancer growth [21]. Numerous *in-vitro* (human lung cancer cell lines- A549, H1264, H1299, Calu-6) and *in-vivo* studies of *Panax ginseng* against lung cancer have been reported indicating its multiple molecular targets of immunomodulation [22]. A nano-particle of *Panax ginseng* using silver has shown cytotoxicity against the A549 cell line (IC₅₀ value 20 µg/mL) by inducing apoptosis *via* the p38 mitogen-activated protein kinase (MAPK)/p53 pathway [23].

These studies indicate that plant secondary metabolites have the potential to modulate the immune system through multitargeted pathways and produce the desired pharmacological action, which is also applicable to treating cancer. This hypothesis has been proved for a few Natural Products such as curcumin, resveratrol, quercetin, genistein, betulinic acid, and zerumbone Fig (1). [24]. This chapter examines numerous secondary metabolites showing anti-cancer activities through immunomodulation Table 1, and the established natural products have been described to the greatest extent possible.

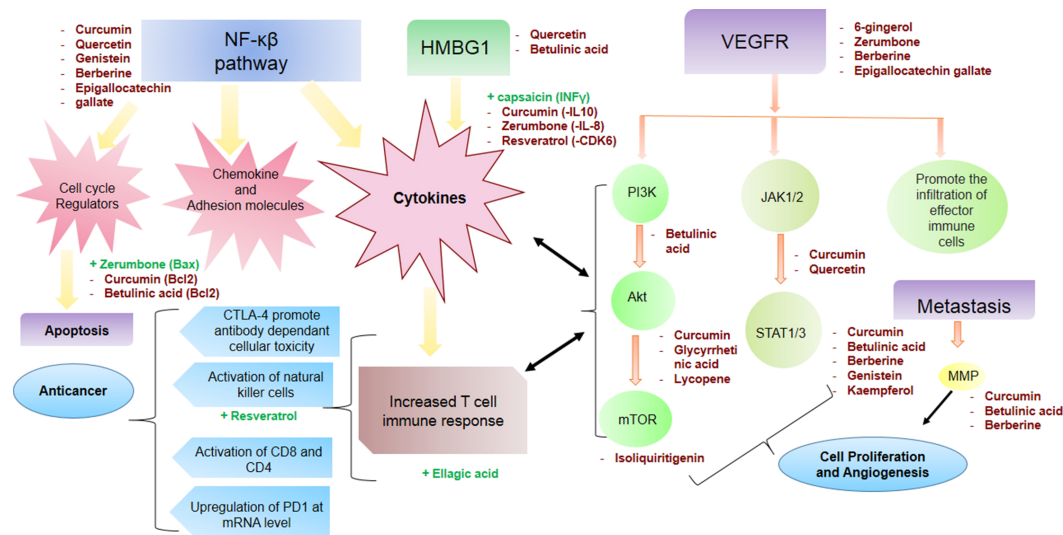


Fig. (1). Anticancer activity of selected natural products *via* immunomodulation (-ve sign indicates inhibition and +ve sign indicates activation).

CHAPTER 8**Natural Immunomodulators for Infections and Other Diseases****Aaliya Liyakath Ali¹, Namrata Nailwal¹, Sujata Sawarkar² and Gaurav Doshi^{1,*}**

¹ Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India

² Department of Pharmaceutics, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India

Abstract: Infection is one of the most common occurring issues in an individual. Diseases caused by infections hamper the immune system of an individual. To modulate the immune system, immunomodulatory drugs work by either stimulating or suppressing the immune system. Several drugs like levamisole and azathioprine are available in the market today to overcome various infections. But an alternative is required to overcome the drug resistance and other side effects associated with these available drugs. To tackle these problems, many plant-based immunomodulators are being explored and have proven to be beneficial against these infections. This chapter focuses on the mechanism of action and application of natural immunomodulators like Curcumin, Resveratrol, and Genistein on various infections. The primary goal of this chapter is to understand the role of natural immunomodulators in the body for various infections and related disease conditions. With the help of findings, one can conclude that all-natural immunomodulators have areas that need attention, including their therapeutic risk-benefit ratio and their target binding affinity for various infections. However, further investigations into these drugs are necessary for a clear understanding to maximize their clinical applications

Keywords: Natural Immunomodulators, Antimicrobial, Antibacterial, Antiviral, Antiparasitic, Ayurveda, Curcumin, Genistein, Immunosuppressants, Immunostimulants, Infection, Resveratrol.

INTRODUCTION

An immune response is the ability of the human body to be shielded, protecting itself against various harmful agents [1]. Immunomodulators are drugs that modify the response of the immune system either by stimulating or suppressing

* Corresponding author Gaurav Doshi: Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India; E-mail: gaurav.pharmacology@gmail.com

the release and production of antibodies in human serum. They are used to restore the level of the immune response [2]. A well-balanced immune system enhances defence mechanisms against various infections, hypersensitivity reactions, and autoimmune diseases. Immunomodulators are used in treating chronic infections, cancer, and organ transplantation [3]. There is a rise in the emergence of novel immunomodulators as the understanding of autoimmune diseases increases globally [4, 5]. Immunostimulants act by showing prophylactic action in normal individuals by activating the primary immune responses [6]. These agents are used in the treatment of inflammation and cancer by enhancing the body's defence mechanism. T and B lymphocytes act as primary targets for immune-stimulating agents. Immunostimulants act by affecting cytokines and specifically inhibiting or enhancing populations of immune cells like lymphocytes, neutrophils, macrophages, NK cells, and cytotoxic T lymphocytes [7].

Immunosuppression mainly decreases the body's resistance to fight against infections [8]. These agents have been clinically used to treat graft rejections and autoimmune diseases and hence are termed antirejection agents [9]. They are the most widely used drug in the treatment of inflammatory bowel disease (IBD) like Crohn's disease [3]. Drugs such as prasterone and hydroxychloroquine are immunomodulators, used to manage immunological conditions like rheumatoid arthritis and systemic lupus erythematosus [10]. The present immunomodulant therapy consists of drugs that have a specific mode of action and give rise to various side effects. Some of the side effects caused by these immunomodulators are pulmonary toxicity, myelosuppression, and hypertension [11]. These adverse effects can often lead to being the cause of death in immunocompromised patients [12]. Cyclosporine is an immunosuppressant that causes adverse effects like hyperkalemia, convulsion and hepatitis when given orally or intravenously. It is not recommended during pregnancy. Other alternatives like tacrolimus and mycophenolate are used instead of cyclosporine, however, they increase the risk of diabetes [13 - 15]. Immunomodulators also manifest oral adverse effects like Sjogren's syndrome and oral lichen planus [16 - 18]. Immunostimulants are a class of immunomodulators that enhance body's resistance against infections, while immunosuppressants are agents that inhibit or suppress the active immune system. Natural immunomodulators have the potential to fight off infections caused by microorganisms like bacteria, viruses, and fungi.

INFECTIOUS DISEASES

Infection is a bodily condition produced by the introduction of one or multiple pathogens like bacteria, fungi, and viruses. The severity of infection can range from mild to severe and sometimes may be fatal. There are four major agents

responsible for infections: Bacteria, fungi, viruses, and parasites, as depicted in Table 1.

Table 1. Various infectious agents and diseases caused by them.

Sr. No.	Type of Infective Agent	Name	Disease	Reference
1	Bacteria	<i>Bacillus anthracis</i>	Anthrax	[19]
2	Bacteria	<i>Mycobacterium tuberculosis</i>	Tuberculosis	[20]
3	Bacteria	<i>Vibrio cholerae</i>	Cholera	[21]
4	Fungi	<i>Pneumocystis</i>	Pneumonia	[22]
5	Fungi	<i>Candida species</i>	Mucocutaneous infections	[23]
6	Virus	<i>Human immunodeficiency virus</i>	Acquired Immuno Deficiency Syndrome (AIDS)	[24]
7	Virus	<i>Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus</i>	Covid-19	[25]
8	Virus	<i>Poliovirus</i>	Poliomyelitis	[26]
9	Virus	<i>Hepatitis virus</i>	Hepatitis	[27]
10	Parasite	<i>Plasmodium species</i>	Malaria	[28]
12	Parasite	<i>Wuchereria bancrofti</i>	Filariasis	[29]

Antibiotics are active drugs that are used to treat various infections. Antibiotics either destroy or prevent the multiplication of microbes, which allows the immune system to clear infections. Antibiotic resistance, these days, is limiting the efficacy of many of these drugs. Using an antibiotic is advised even after no more symptoms are seen to heal the infection and prevent the growth of resistant microbes. Antibiotic development presently focuses on targets that are critical for bacterial metabolism; however, studies into how bacterial species communicate with one another could lead to the creation of newer medications that reduce resistance. Antibiotics are not effective against infectious diseases caused by viruses like influenza; instead, antiviral drugs are used for viral infections. These drugs elicit their therapeutic effect either by limiting or hampering the multiplication capacity of the virus or by increasing the immunological response of the body to the infection. Antiviral drugs are divided into various categories, each of these is used to treat different types of viral infections, including influenza, HIV, herpes, and hepatitis B. Viruses, similar to bacteria, evolve throughout time and become resistant to antiviral medications [30]. Several studies have looked at the current state of immunomodulatory techniques for infection prevention in neonatal immunological deficiencies and recent

CHAPTER 9

Delivery of Immunomodulators: Challenges and Novel Approaches

Mansi Damani¹, Prabha Singh¹ and Sujata Sawarkar^{1,*}

¹ Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, University of Mumbai, India

Abstract: Immunomodulators can be either synthetic in origin or naturally obtained. Natural plant-based compounds can influence the immune system by either affecting antibody secretion to control the infection or affecting the functions of immune cells, thus contributing to maintaining immune homeostasis. Phytochemicals in plants, such as polysaccharides, lactones, flavonoids, alkaloids, diterpenoids and glycosides, have been reported to possess immunomodulating properties. However, there are many challenges limiting the clinical use of natural immunomodulators. In this chapter, we have discussed in detail standardization, formulation development, route of administration and regulatory concerns of natural immunomodulators. In order to overcome these challenges and ensure that natural immunomodulators reach the target site at therapeutic concentrations, different polymer and lipid-based nanocarrier delivery systems have been developed. These nanocarriers by virtue of their size, can easily penetrate and reach the target site and deliver the drugs. Many nanocarriers like liposomes, niosomes, nanoparticles, microemulsions, phytosomes and other vesicular systems designed for natural immunomodulators are discussed in this chapter.

Keywords: Drug Delivery Challenges, Drug Delivery Systems, Immunomodulators, Immunostimulants, Immunosuppressants, Immunoadjuvants, Nanocarriers, Natural Products, Phytoconstituents.

INTRODUCTION

Immunity is the ability of the body to combat a wide array of potential pathogens, resist diseases and prevent any organ or tissue damage. It comprises of series of balanced complex, multicellular and physiologic mechanisms that enable the host body to differentiate between self and foreign entity and eliminate it [1, 2]. Vertebrates have an extremely complex and advanced immune system, which is capable of producing a large variety of cells to arrest the growth of various microbes and the development of subsequent infections. The immune system is

* Corresponding author **Sujata Sawarkar**: Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, University of Mumbai, India; E-mail: sujata.sawarkar@bncp.ac.in

not confined to any particular organ or tissue; rather, it is active for the entire body of the host. The immune system is simply a collaborative amalgamation between cells and proteins that work systemically to provide protection against infection or any foreign entity [3].

The development process of all immune cells originates from hemopoietic stem cells in the bone marrow. These cells either migrate to the thymus and differentiate into mature T-lymphocytes (T-cells) or remain in the bone marrow to differentiate and mature into B-lymphocytes (B-cells). B-cells differentiate into plasma cells, eventually producing immunoglobulins or antibodies. In a mature state, B-cells are generally found in bone marrow, spleen, intestine, lymph nodes and bloodstream. On interaction with a foreign entity or an antigen, B-cells mature into plasma cells and produce highly specialized serum protein molecules to destroy antigens; B-cells also mature as memory cells to ensure a quick response to the same antigen if the infection is encountered again. After leaving the thymus, T-cells populate either in the spleen, bone marrow, lymph nodes or blood and further mature into cytotoxic T-cells and helper T-cells for exhibiting cell-mediated immune response. T-cells have antigen-specific molecules that help them recognize and eliminate specific antigens. Helper T cells assist B-cells to produce antibodies and assist killer T-cells in their attack on foreign entities [4].

Immunity is categorized as active immunity and passive immunity. When immunity is achieved by exposure to a disease organism triggering the host immune system, it is an active type of immunity. This type of immunity is long-lasting and involves memory B-cells. Natural active immunity is achieved when the body is exposed to an infection or by introducing killed or attenuated forms of the disease pathogens through vaccination, called induced active immunity. Passive immunity is acquired when antibodies are directly provided to an individual without involvement or activation of the immune system. Natural passive immunity is attained from the mother to her child by the passage of antibodies either through the placenta or through breast milk. Passive immunity is transient in nature and lasts only for a few weeks to months but provides immediate protection in contrast to active immunity, which develops after a longer period of time, however, it is long-lasting [5, 6].

Over the past few decades, the health industry and biomedical research have collectively emphasized the importance and maintenance of the healthy immune system for prevention against various infections and rapid recovery from diseases. Ironically, immunity is not always as beneficial to the host body, especially when it causes tissue damage, hypersensitivity and or leads to other autoimmune diseases. In such cases, it becomes necessary to modulate immunity by suppressing it in order to treat autoimmune diseases or prevent graft rejection. On

the other hand, in infectious and by enhancing immunity to fight off infections. Over the years, research has led to the development of a group of molecules that can target the immune system [7, 8].

NATURAL IMMUNOMODULATORS

Synthetic and chemical immunomodulating drugs have been used to treat cancer, graft rejections and other autoimmune disorders for years. For example, cyclophosphamide is a widely used alkylating agent that acts as an immunosuppressor against animal and human malignancies. It has the tendency to inhibit both humoral and cell-mediated immune responses. Cyclophosphamide, however, is associated with renal toxicity and renal failure. Synthetic immunomodulators are often associated with nephrotoxicity, hypertension, hepatotoxicity, hirsutism, gastrointestinal toxicity (nausea, vomiting, diarrhea, anorexia and abdominal pain), neurotoxicities such as headache, insomnia, pain, cardiovascular toxicity and metabolic toxicity like hyperkalemia, hypomagnesemia, hyperglycemia *etc.* Drugs like azathioprine used as a disease-modifying anti-rheumatic drug (DMARD) also affect rapidly growing cells, including bone marrow and gastrointestinal cells resulting in thrombocytopenia, leucopenia and gastrointestinal toxicity. Anti-thymocyte globulin, synthetically prepared polyclonal IgG component from the serum of various animals used in the treatment of renal allograft rejection causes serum sickness and nephritis. Some of the chemical immunomodulators also cause fever, leucopenia, thrombocytopenia, skin rashes and infertility due to the destruction of testicular and ovarian cells [9].

Clinical drawbacks and limitations of synthetic immunomodulators have led to increased interest in the study of natural and plant-based immunomodulators. Studies have indicated that many natural products have the ability to repair impaired immune systems either by activating the components of innate immunity, such as stimulation of macrophages and lymphocytes, or by modulating the cytokine profile and stimulating the process of apoptosis, thus reducing the incidence of infections. Natural immunomodulators can help potentiate humoral immunity (HI) or cell-mediated immunity (CMI) by causing a significant increase in serum immunoglobulin (Ig) levels and other mediators of CMI in various body fluids. Natural products also cause a significant increase in the populations of mature T cells, interleukins, tumor necrosis factor-alpha (TNF- α), interferons, *etc.* Natural immunostimulants can also activate humoral as well as cell-mediated immune response against tumors facilitating recognition and destruction of the tumor, and enhancing the ability of the host to tolerate damage caused by toxic chemicals [1].

Marketing Strategy & Regulatory Perspective for Natural Immunomodulators

Alveera Ansari¹, Namrata Nailwal¹, Sujata Sawarkar² and Gaurav Doshi^{1*}

¹ Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India

² Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W), Mumbai-400056, Maharashtra, India

Abstract: Many natural products, such as *Azardicaindica*, *Curcuma longa*, and *Ocimumsanctum*, are often used as immunomodulators. The increased prevalence of chronic diseases, along with the negative effects of synthetic immunomodulators, has resulted in the establishment of a global natural immunomodulator market. For researchers, complementary and alternative medicine provides a new target for drug discovery approaches and medication development. Ayurveda, Homeopathy, Naturopathy, and the Chinese medicine system are examples of complementary and alternative medicine approaches. Phytoconstituents with therapeutic action are included in the Complementary and Alternative Medicine (CAM) categories of natural goods. In Europe, natural immunomodulators are considered food supplements, while in the United States, they are utilized as dietary supplements. In India, it is controlled by the Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy). With the help of the literature findings, we understand that even natural phytoconstituents also require and must undergo well-defined regulatory approval processes to launch in the market. But the regulation slightly differs as per the country and region. With the help of all the findings, one can conclude that the regulation of natural immunomodulators is equally important to set its marketing strategies as well as for its post-marketing surveillance as compared to the synthetic molecules. With this objective, the primary goal of this chapter is to draw more attention to the regulatory aspects of natural immunomodulators by comprehending the information on natural immunomodulator marketing strategy as well as the legislation that governs it.

Keywords: Guidelines, Legislation, Marketing Strategies, Natural Immunomodulators, Regulatory Agencies.

* Corresponding author Gaurav Doshi: Department of Pharmacology, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India; E-mail: gaurav.pharmacology@gmail.com

INTRODUCTION

Immunomodulators can help combat and mitigate diseases and illnesses caused by immunodeficiencies [1 - 6]. Several metabolites that decrease immune responses may be effective in the treatment of autoimmune illnesses [7, 8]. Reactivation of latent Tuberculosis (TB) is another documented unfavorable effect, particularly in association with new-generation immunomodulatory medicines [9, 10].

Pharmaceutical drug laws, commonly called pharmaceuticals regulatory guidelines, are a collection of authorized, procedural, and technical requirements used by government agencies to guarantee patient safety, drug efficacy, and purity, as well as the reliability of the product. The word “regulation” encompasses comprehensive elements (for example, rules, recommendations, processes and policies) with varied legal bases and jurisdictions [3, 4]. This is achieved by a variety of regulatory processes performed throughout the life cycle of drug discovery and development, which includes premarket screening and analysis of new medicines, an inspection of manufacturing facilities, legislation, marketing, and post-market surveillance. Each country has unique rules that govern invention, production, screening, advertising, and post-marketing research. The goal is to keep drug standards high at all times to meet the needs of health maintenance of each country [5].

In India, the regulatory bodies are the Central Drug Standard Control Organization (CDSCO), the Indian Council of Medical Research (ICMR), and the Ministry of Health and Family Welfare (MoHFW). The CDSCO is responsible for carrying out the tasks delegated by the Central Government under the jurisdiction of the Drugs and Cosmetics Act. It is responsible for guaranteeing the quality, usefulness, and purity of medications distributed to the public at both the federal and state levels. CDSCO is in charge of drug importation, new drug authorization, clinical trials, and meetings of the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC). The CDSCO plays a key role in approving specific licenses through the Central Licensing Approval Committee. ICMR is considered one of the oldest clinical study organizations in the world and the best framework in India to design, coordinate, and promote biomedical studies. The organization is supported by the Government of India through the Department of Health and Family Welfare [6, 7]. The Union Health Minister is in charge of the governing body. The Scientific Advisory Board comprising notable professionals in the field of life sciences and biomedical areas, advises the CDSCO on technical and scientific concerns [8, 9].

The US Department of Health and Human Services (HHS) is the primary organization in charge of preserving the health of all Americans and providing

basic humanitarian assistance. HHS has 11 operational departments, including eight US public health services agencies and three human services agencies. These departments offer a wide range of health and human services, as well as life-saving scientific studies. The Food and Drug Administration (FDA) is among 11 agencies within the Department of Health and Human Services responsible for ensuring that the product is healthy and genuine. FDA authenticates the quality and confirms that animal and human medicament, biopharmaceuticals, and surgical instruments are medically beneficial, and computerized devices emitting radiation are harmless. The FDA is divided into five offices that handle various functions: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, Operations and Policy, and Planning, Legislation, and Analysis.

The Centre for Drug Evaluation and Research (CDER) is a department of the Division of Medical Products that regulates biological therapeutics and generic pharmaceuticals. The CDER plays an important role in public health by ensuring that safe and effective medications available to help people in the United States live healthier lives. CDER regulates over-the-counter and prescription pharmaceuticals, including biological therapies and generic drugs, as part of the US Food and Drug Administration (FDA). CDER The Center for Drug Evaluation and Research has twelve separate offices. There are several types of the department, each of which has its subsection. To sell medicinal products or drugs in the United States, pharmaceutical companies must first obtain the product cleared by the US FDA. Each product must go through a rigorous certification process established by the Centre for Drug Evaluation and Research to receive approval [10, 11].

Apart from India and America, “The Pharmaceutical and Food Safety Bureau” (PFSB) of the Ministry of Health, Labour, and Welfare (MHLW) is the pharmaceutical regulating authority of Japan. The Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) is the decision body concerned with new drug approvals [12, 20]. The Organization for Pharmaceutical Safety and Research (OPSR), often known as “KIKO or “the DO” (Drug Organization), is an independent entity affiliated with MHLW, responsible for negotiating drug development projects with companies. The GCP (Good Clinical Practice) guideline will improve the ethical and scientific quality of studies conducted in Japan. It may also improve relationships between medical professionals and patients if the requirement for explicit informed consent in clinical trials leads to the provision of a comparable level of patient information in routine care and changes physicians' traditional paternalistic attitude toward patients. The GCP guideline was implemented in Japan in 1997. International Council for Harmonization-Efficacy guidelines (ICH-E6), sometimes known as “the new

Natural vs. Synthetic Immunomodulators

Girish B Mahajan^{1,*} and Lakshmi Balachandran²

¹ HiMedia Laboratories Pvt Ltd, Maharashtra, India

² Freelance Medical Writer, Maharashtra, India

Abstract: Immunomodulators are key components in deciding immunity status and development in an individual. The topic has been under more emphasis, especially during and after the COVID-19 pandemic phase. Several plants with medicinal potentials are appreciated in traditional medicines for their healing perspective and have been technically examined for their immunomodulation potential. A number of plant-based bioactive compounds have been extracted and purified with such bioactivities that can rationalise their usage in conventional medication in the past and can stimulate further research in the future as well. Synthetic immunomodulators are significant for generating remedial or prophylactic formulations with defined chemical ingredients from regulatory perspectives. The review highlights the key immunomodulators, both synthetic and natural, until 2020. It also emphasises on market potential and commercial aspects of these. We have explained and listed several plants and their active scaffolds having immunomodulation activities along with synthetic compounds with similar bioactivity. We envisage the review to be an organised compilation and comparison of natural and synthetic immunomodulators and also focus on new chemical immunomodulator scaffolds.

Keywords: Adjuvant, Antibody-Mediated Immunity, Cell-Mediated Immunity, COVID-19, Humoral, Immunity, Immunology, Immunomodulators, Innate Immunity, Immuno-Stimulants, Plant Extracts, Synthetic Immunomodulator, Synthetic Immunomodulator, Traditional Medicine.

INTRODUCTION

The Nature of the Immune Response

In a world where we are faced with an environment that is host to innumerable microbes and toxic molecules, a functional immune system is paramount to homeostasis and good health. The environment is inhabited by commensals, parasites, toxins and various pathogens, and the pathogens continuously evolve

* Corresponding author Girish B Mahajan: HiMedia Laboratories Pvt Ltd., Maharashtra, India;
E-mail: girishbm2000@gmail.com

with their myriad mechanisms to invade, replicate, spread, and affect the normal host functions. Phagocytic cells, like macrophages & neutrophils, cytokines, interferons, natural killer cells, and complements comprise the primary wall of our defence. These are non-specific or generalised defence mechanisms, aimed at localizing the foreign elements and eliminating them. The second wall of defence assumes some specificity. Lymphocytes and other substances such as cytokines and antibodies, and the macrophages present the antigens to two distinct types of cells: Thymus derived cells (T-cells) and Bursa derived cells (B-cells). Each lymphocyte recognizes an Immunogen. The combination of cell and antibodies-mediated immunity together accounts for combating the majority of microbes, such as fungi (both spores & mycelia), bacteria, viral particles, many parasites, cancer-induced cells, *etc.* The tertiary wall of immunity is the concerted action of innate immune responses and the products of particular acquired immunity activities.

Widely touted as the “Drugs of the 90s” immunomodulators are biological response modulators [1]. Optimum health depends on the ability of the defence mechanism to discriminate between “self (own)” and “non-self (foreign)” molecules, cells as well as tissues. The human immune response is a systematic, organized, three-layered defence mechanism comprising of both cellular and humoral immune responses.

An immunomodulator can be any substance of natural or man-made origin that can kindle, subdue, or modify the immune reaction. This includes the innate response and the adaptive reactions, too [2]. Immunosuppressants are antagonists of the immune system [3], and help prevent the rejection of implanted organs and tissues, and in controlling autoimmune disorders [4]. Many implant centers use multiple drugs, each targeted at a specific location in the T-cell activation cascade. They can generally be classified as transcription inhibitors, nucleotide synthesis inhibitors, growth factor signal inhibitors, and differentiation inhibitors. Polyclonal anti-lymphocyte antibodies, monoclonal antibodies targeted to the T-cell antigen receptor complex (OKT3, TI0B9), and monoclonal antibodies targeted to more cellular antigens, including interleukin-2 receptor alpha, which pay special attention to immune cell responses and are used as ingestion therapy and/or antidepressants, in clinical practice [5]. Immunoadjuvants are specific immune stimulants that improve immunity, especially for vaccine's efficacy [3]. They promise to be a true module for the immune response. Immunostimulants activate both innate, innate arms and flexible responses. They play a dual role depending on a person's immune system. In healthy people, they act as immunopotentiators, and in those with weak immune responses, they act as immunotherapeutic agents. Immunostimulators, in particular, are responsible for

the antigen-dependent stimulation of granulocyte and macrophages, and have a positive effect on their function [6 - 8].

NATURAL IMMUNOMODULATORS (NI)

The immune response can be altered by the host's natural resources or by external products from various sources.

Natural immunomodulators of exogenous types have been used to modulate immune response since antiquity. Traditionally, ancient Indian medicine uses plant products to modulate the immune response, as immunostimulants as well as immunosuppressors. For the past few decades, new healthcare challenges have emerged in the form of multidrug resistance of pathogens, against empirically used antibiotics. This “dark age” of antibiotics has propelled new research on immunomodulatory agents from plant, fungal, and microbial origin. This has negated the beneficial effects of the “golden era of antibiotics”. It is believed that there were ample forebodings of this situation, even before the discovery of the “Selman Waksman” antibiotics. It is disappointing to note that modern techniques in drug modelling and design have not impacted the pipeline in a massive way, as compared to the number of anti-microbial agents discovered around half a century ago. The future of combination therapy was evident much before [9].

Natural immunomodulators possess a low level of clarity in their action as compared to antibiotics. However, the current worldview is in favor of combination therapy that targets two or more specific sites in the immune system. Around 75% of the global population depends on traditional healthcare remedies. Traditional medicine relies mainly on natural sources as therapeutic and healing agents. Currently, many phytochemicals with therapeutic potential have been identified and used as immunomodulators [10].

Rasayana [10]

The word Rasayana, a combination of two words (*rasa* and *ayana*), refers to nutrition and its transportation throughout the body. Rasayana therapy enhances the qualities of *rasa*, enriching it with nutrients so one can attain longevity, improved memory and intelligence, freedom from disorder, youthfulness, excellence of hair, complexion and voice, optimum development of the physique and sense organs, mastery over phonetics and brilliance. As a dedicated stream of medication for immune promotion, antidegenerative and rejuvenating health care, the Rasayana therapy of Ayurveda is known to prevent the effects of ageing and improve the quality of life for healthy as well as diseased individuals. Rasayana is helpful to improve immunity and is normally advised during the degenerative phase of life, which starts from around 45 years in both males and females [10].

CHAPTER 12**Future Path and Perspectives of Immunomodulators****Megha Karne¹, Supriya G. Jagtap², Sujata Sawarkar³ and Vandana S. Nikam^{1,*}**

¹ Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India

² Department of Pharmacognosy, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India

³ Department of Pharmaceutics, SVKM'S Dr. Bhanuben Nanavati College of Pharmacy, Mithibai Campus, Vile Parle (W), Mumbai-400056, India

Abstract: Immunity is the inherent ability of the body to fight against various infections, and foreign invaders. When the host body comes in contact with a foreign body, a series of chemical mediators are released, which collectively elicit an immune response. The biomolecules capable of stimulating, suppressing and modulating innate or acquired immunity, biological or synthetic in origin, are termed as immunomodulators or immunoaugmentors. Limited clinical use of synthetic immunomodulators has attracted the attention of researchers toward immunomodulatory characteristics of natural therapeutics. Though natural immunomodulators render their efficacy in several chronic illnesses, there are challenges that need to be addressed and resolved to make them viable alternate therapeutics. This chapter highlights the challenges and future perspectives of natural immunomodulators.

Keywords: Adaptive Immunity, Future Challenges, Innate Immunity, Immunomodulators, Novel Drug Delivery, Perspective of Immunomodulators.

INTRODUCTION

The immune system is one of the most crucial systems in the body for survival, as stated in previous chapters. It acts as a defensive system to protect the body from harmful agents and infections. It executes its service through coordinated efforts of a wide range of immune cells having specific, defined roles. The immune system discriminates between harmful and benign foreign invaders, eliminating

* Corresponding author Vandana S. Nikam: Department of Pharmacology, STES's Smt. Kashibai Navale College of Pharmacy, Kondhwa, S. P. Pune University, Pune, Maharashtra, India; E-mail: vandananikam@sinhgad.edu

them from the host system. The immune system is a complicated organ system next to the nervous system in biology.

The complexity of the immune system is observed at many levels. First, the cells of adaptive and innate immunity are interdependent and interconnected. The lymphocytes of the immune system present in a range of differentiated cell states, and they offer adaptive immunity with the help of countless cells of innate immunity.

Second, a complex network of intra- and inter-signaling pathways is operative in immune system functioning. Some of the factors that add to the complexity of the immune system are the process of immune cells education through clonal selection, cell receptors diversity, migration of cells, lymph dissemination throughout the host body, attaining immune homeostasis *via* regulating an ever-changing environment are some add to the complexity of the immune system.

Lastly, lymphocyte specificities, several recognition elements of innate immunity, depict the next level of complexity of the immune system. The feedback mechanism and regulation of immunostains is an intricate, subtle, and complex process and contributes significantly to immunity services.

THE COMPLEXITY OF INNATE AND ADAPTIVE IMMUNITY

The main four networks such as transcriptional, translation, spatiotemporal, and functional, control the overall execution of innate immunity in our body. These networks hold diverse information, including DNA sequence, RNAs, translocation information, spatiotemporal information of protein, subcellular structural details, and signaling process. Moreover, the intercellular communication networks include interactions between host and pathogen, soluble mediators like cytokines channelized linkages between a diverse pool of immune cells and other cells of tissues. The function of the immune system is quite dynamic, resulting in the non-linear behavior of several components, their interactions, feedback regulatory mechanisms, and three-dimensional positioning [1 - 4].

The major hurdles in the quantitative measurement of immune system components are complex and overlapping networks. With the advancement in analytical tools, genomics, proteomics, metabolomics, and cutting-edge technology, it would be possible to reach the depth and girth of the immune system and evaluation of natural immunomodulators. The involvement of sophisticated live and static imaging techniques with novel immunological assay warranted unraveling the complexity in the intracellular networks of the immune system.

Approaches and Challenges in Standardization of Natural Immunomodulators

Natural drugs and their phytoconstituents with potential immunomodulation activity are gaining popularity owing to new immune disorders and illnesses. In addition, complexities in the phytoconstituents have always presented challenges for the standardization of these compounds. It becomes necessary to provide sufficient preclinical data before natural medicines are subjected to clinical trials [5]. These strategies could be promising, allowing the development of new promising bioactive molecules. Within this context, an approach has been illustrated below with the studies conducted on many plant-origin drugs.

A major source of concern is the lack of consistency in pharmacological responses induced by plant extracts. This could be explained by the secondary metabolites' classic reliance on changes in the environment, which could also disrupt the repeatability of the end result with the extracts. Furthermore, the steadiness of therapeutic dose is among the main challenges that researchers face, as the amount of bioactive components generated differs due to the geographic area and ecological elements. Such issues can be resolved if the standardization principles of extracts and enriched fractions are systematically urged for all analytical studies.

The experimental investigation information recorded from immunomodulatory studies of *Phyllanthus* evidences an enthusiasm for identifying new chemical constituents from the available natural assets that can probably adapt to the immune responses of the human system. However, the challenges that are associated with the potential application of extracts of varied *Phyllanthus* species and the bioactive compounds as immunomodulators need to be examined.

The bio-active components of *Phyllanthus* species, namely phyllanthin, hypophyllanthin, ellagic acid, gallic acid, corilagin, niranthin, and geraniin, are highly variable in their expressions of quantity achieved at different elevations, which makes it challenging to retain quality in each batch.

The characterization of bioactive components responsible for the immunomodulation activity of plant extracts, as well as qualitative and quantitative evaluations of the chemical biomarkers for standardization and establishing the basic mechanisms of action, should have been the focus for future investigation into *Phyllanthus* species.

Earlier research studies have reported the contradictory effects of *Phyllanthus* extracts on immunomodulating activity. Very few studies have been performed on

SUBJECT INDEX

A

- Acid 94, 96, 141, 142, 144, 151, 152, 220, 230, 260, 383, 402
- ascorbic 94, 96
- caffeic 155, 157, 158, 249
- chebulagic 151, 152, 260
- eicosapentaenoic 372
- ellagic 141, 142, 144, 220, 230, 260, 383, 402
- Glycyrrheticin 96, 141, 157, 158, 201, 221, 231, 260, 280, 288, 291, 292, 298, 380, 381
- hyaluronic 288
- hydrocyanic 380
- hypochlorous 201
- oleanolic 221, 280, 381
- orthophosphoric 141
- rosmarinic 157, 158
- stearic 291, 292, 294, 298
- tannic 260
- tetrahydrofolic 96
- tinosporic 381
- ursolic 291, 381
- Acquired immuno deficiency syndrome 246
- Adaptive immune system 5, 16, 20, 22, 57, 64, 68, 166, 169, 191, 192
- Adenosine deaminase 43
- Adjuvant therapy 31, 217
- Advisory committee on medical devices (ACMD) 332
- Agents 67, 77, 99, 165, 166, 167, 169, 172, 200, 203, 244, 245, 370, 382, 387, 388
- anti-angiogenic 169
- anti-inflammatory 99
- chemoprotective 77
- chemotherapeutic 67
- immunotherapeutic 370
- Agranulocytosis 385
- Aicardi-Goutieres syndrome 45
- Aldrich syndrome 46
- Allergic 23, 27, 48, 49, 171, 258
- diseases and disorders 48
- rhinitis (AR) 23, 27, 48, 49, 171
- skin diseases 258
- Allergy-related diseases 22
- Anaphylaxis reactions 207
- Antibacterial 103, 248, 249, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261
- activity 248, 249, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261
- properties 103, 259
- Antibody 128, 199, 369
- dependent cellular cytotoxicity 128
- forming cells (AFCs) 199
- mediated immunity 369
- Antifibrinolytic activity 127
- Antifilarial activity 128
- Antifungal activity 248, 249, 250, 251, 252, 253, 254, 256, 259, 260, 261
- Antigen-presenting cells (APCs) 15, 16, 68, 93, 192, 199, 208, 384
- Anti-inflammatory 63, 78, 128, 136, 255, 289, 297, 372
- activity 78, 128, 289, 297
- effects 63, 136, 255, 372
- Anti-inflammatory drugs 196, 202
- non-steroid 196
- Antimicrobial activity 251, 252, 253, 258, 259, 307
- Antioxidant proteins 178
- Antiparasitic activity 250, 252, 253, 254, 255, 256, 258, 259
- Antitumor activities 230, 302, 375
- Antiviral efficacy 261
- Apoptosis 12, 20, 52, 53, 56, 66, 96, 172, 224, 230, 255
- Arthritis 26, 60, 183, 210, 303
- chronic 207
- collagen-induced 151, 208
- mediated autoimmune 207
- proteoglycan-induced 210

- Asthma 22, 23, 98, 118, 136, 144, 174, 183, 258, 261, 379, 410
 bronchial 118
 conjunctivitis 22
 Atherosclerosis 100, 382
 ATM protein 47
 Autoimmune 24, 33, 34, 41, 42, 46, 53, 55, 59, 97, 101, 190, 191, 193, 195, 199, 203, 209, 210, 212, 245, 277, 325, 385, 386
 diseases (ADs) 41, 42, 53, 55, 190, 191, 193, 209, 210, 212, 245, 277, 385
 disorders 33, 34, 53, 55, 59, 97, 101, 190, 195, 199, 203
 hemolytic anemia 209
 illnesses 210, 325
 kidney disease 386
 lymphoproliferative syndrome 46
 neutropenia 24
 thyroiditis 209
 Autoimmunity 41, 42, 43, 45, 46, 51, 54, 55, 172
 infection-related 55
 Auto-inflammatory diseases 33, 43, 60, 61, 62
 Autosomal recessive transmission disease 61
- B**
- Bacteria 2, 119, 247, 307
 aerobic 307
 aerobic spore-forming 119
 antibiotic-resistant 247
 disease-causing 2
 Bechet's disease 64
 Betulinic acid 217, 219, 225, 226, 232
 Bone marrow-derived macrophages (BMDM) 194
 Bradykinesia 58
- C**
- Cancer 31, 33, 34, 41, 65, 66, 67, 68, 83, 84, 171, 176, 199, 217, 218, 222, 224, 225, 231, 245, 380, 385, 406
 breast 149, 224
 colon 385
 hepatic 231
 immunotherapy 33, 41, 66, 176, 406
 metastatic colorectal 225
 prostate 224, 380
 Carbonic anhydrase inhibitors 52
 Cardiothoracic surgery 47
- Cell-mediated 4, 18, 95, 122, 127, 177, 278, 369
 immunity (CMI) 4, 18, 95, 122, 127, 177, 278, 369
 phagocytosis 127
 Chemokines release 27
 Chemotaxis 11, 26, 143
 Chinese 119, 227, 352
 herbal pharmacopoeia 119
 medicines 227, 352
 Chronic lymphocytic leukaemia 48
Clostridium perfringens 254
 Collagen-induced arthritis (CIA) 151, 208
 Combination therapy 371
 Complementary and alternative medicine (CAM) 249, 324
Coptis chinensis 220, 227
 Coronary artery disease (CAD) 376
 Coronavirus 176
 Corticosteroids, systemic 53
 COVID-19 92, 167, 387, 404
 crisis 387
 infection 404
 pandemic 167
 vaccines 92
 Coxsackie virus 261
 Crohn's disease 245, 384
 Cytokine(s) 30, 61, 64, 94, 97, 101, 172, 174, 177, 221, 375, 404
 anti-inflammatory 30, 64, 97, 172, 174, 221
 growth-promoting 167
 inflammatory 57, 61, 94, 101, 177, 375
 signaling pathways 61
 storm syndrome 404
 Cytomegalovirus 48, 255

Subject Index

Cytometric bead assay 183
Cytotoxic coumarins 78, 375
Cytotoxicity 25, 193, 194, 195, 200, 217, 218, 219, 221, 298, 299, 307, 405
 and immunomodulating effects on
 monocytes 405
 antibody-dependent cell-mediated 25
Cytotoxic 14, 383
 lymphocytes 383
 proteins 14

D

Deficiency 43, 122, 246
 immune 122
 immunological 246
 severe combined immune 43
Delayed type hypersensitivity (DTH) 135, 137
Dendritic cells (DCs) 10, 12, 14, 15, 88, 89, 95, 97, 166, 168, 191, 248, 253
Diphtheria disease 32
Disease(s) 77, 209, 218, 387, 407, 411
 cancer-related 387
 cardiovascular 218
 fibrotic 209
 heart 77
 immune-related 407, 411
 lymphoproliferative 209
 modifying anti-rheumatic drug (DMARD) 278
Disorders 30, 33, 42, 43, 44, 45, 46, 47, 56, 68, 138, 261, 304, 405
 congenital 47
 immune-compromised 405
 immune-related 405
 immune system-related 68
 immunodeficiency 42, 43, 44, 45, 46
 metabolic 33
 neurodegenerative 30, 261
 rheumatic 138, 304
 thyroid-affecting 56
Downregulate signaling pathways 170
Droplet counter-current chromatography (DCCC) 180

Natural Immunomodulators 415

Drug(s) 47, 48, 64, 96, 110, 111, 118, 190, 224, 28, 244, 245, 262, 278, 288, 289, 290, 291, 295, 299, 303, 306, 330, 332, 333, 334, 339, 341, 347, 359, 385, 405
 allopathic 111
 anti-allergic 190
 anticancer 224, 228
 anti-epileptic 47
 antihelminthic 385
 antiproliferative 385
 chemotherapeutic 48
 chemotherapy 96
 disease-modifying anti-rheumatic 278
 hydrophobic 291, 299
 immune 262
 immune-therapeutic 405
 immunosuppressant 64
 metabolizing enzymes (DMEs) 172
Dysfunction 30, 53, 59, 103, 212, 218
 autonomic 59
 cognitive 212
 sexual 218

E

Ectodermal dystrophy 45
Effects, immune-modulatory 86
EGFR signalling pathways 231
Eholanthrene-induced sarcoma 128
ELISPOT assay 199
Enzymes 66, 77, 97, 100, 122, 173, 255, 376
 drug-metabolizing 172
 hydrolytic 6, 86
 linked immunosorbent assay 151
 lysosomal 10, 23
 mevalonate kinase 61

F

Fever 49, 91
 hay 49
 yellow 91
FHL syndromes 45
Fibrosis, myocardial 210

Folate deficiency 99
FTIR 154, 156
 analysis 154, 156
 spectrometer 154
Functions 61, 76, 96
 immune system's 76
 leukocyte 96
 mitochondrial 61

G

Gas chromatography 115
Gastrointestinal 85, 308
 environment 308
 microflora 85
Genotoxicity 172
Glioblastoma 293
Gut microbiota 85, 99

H

Haemolytic disease 23
Hashimoto's thyroiditis (HT) 56, 208
Heat shock proteins 16, 93, 171
Hepatitis 31, 48, 52, 76, 101, 141, 245, 246,
 252, 256
 virus 246
Hepatocellular carcinoma 224
Hepatotoxicity 172, 278, 388
Herbal 336
 medications 336
 Medicinal Products (HMPC) 336, 338, 344,
 346, 351
Herpes simplex encephalitis (HSE) 45
High 114, 115, 118, 130, 131, 132, 135, 142,
 150, 152, 154, 158, 180, 182
 pressure liquid chromatography (HPLC)
 114, 115, 118, 130, 131, 132, 135, 142,
 150, 152, 154, 158, 180
 resolution mass spectrometry (HRMS) 182
 speed counter-current chromatography
 (HSCCC) 180
High-performance 114, 115, 118, 140, 158,
 180, 181

capillary electrophoresis (HPCE) 181
liquid chromatography 118, 180
thin layer chromatography (HPTLC) 114,
 115, 140, 158, 180

Histiocytosis 48
HPLC technique 145, 147
Human 15, 16, 52, 53, 86
 leukocyte antigen (HLAs) 15, 16, 52, 53
 peripheral blood mononuclear (HPBM) 86
Hydrastis canadensis 227
Hyperglycemia 278

I

Immune 24, 28, 42, 52, 55, 68, 88, 94, 152,
 209, 212, 277, 278, 388, 401
 cells migration 152
 checkpoints 68
 diseases 42, 55
 disorders 42, 209, 388
 homeostasis 28, 88, 401
 mediated disease 52, 212
 response, cell-mediated 94, 277, 278
 thrombocytopenia 24
Immune system 41, 58, 247
 acquired 41, 247
 dysregulation 58
Immunity diseases 144
Immuno 68
 checkpoint inhibitors 68
 modulating therapy 68
Immunodeficiency syndromes 42
Immunosuppressive properties 386
Immunotherapy in cancer and autoimmune
 disorders 34
Inflammation, immune complex-mediated
 acute 205
Inflammatory 6, 8, 14, 23, 30, 49, 50, 57, 97,
 103, 191, 200, 209, 245, 304, 374
 bowel disease (IBD) 30, 97, 245
 diseases 209, 304
 responses 6, 8, 14, 23, 49, 50, 57, 103, 191,
 200, 374
Inhibition, tyrosinase 78

Subject Index

Injuries 100, 210, 293
 cardiac 210
 ischemia-reperfusion 100
 paracetamol-induced liver 293
Insomnia 278, 388
Intracellular adhesion molecules (ICAMs) 173
Irritable bowel syndrome 379
Ischemia-reperfusion injury (IRI) 100

J

Japanese encephalitis 256
 virus (JEV) 256

K

Kidney transplants 167
Kupffer cells 198

L

Leucopenia 167, 176, 278, 382
Lipopolysaccharide, bacterial 166, 194, 197,
 208
Lipoxygenase 248, 375
Liver 124, 175, 183, 251
 cirrhosis 175, 183
 diseases 124, 251
Lower respiratory tract infection (LRTI) 95,
 98, 101
Lycium barbarum polysaccharide (LBP) 306

M

Major histocompatibility complex 15, 52, 53,
 192, 208, 211
Methods, spectrophotometry 113
Mitogen-activated protein kinase (MAPK)
 219, 231, 256, 403
Mucosal 3, 87, 90
 associated lymphoid tissue (MALT) 3
 immune system (MIS) 87, 90

Natural Immunomodulators 417

Multiple sclerosis (MS) 55, 57, 59, 60, 97,
 150, 182, 385, 410
Mycobacterial disease 45

N

Nanoparticles 294, 295
 metal 294, 295
 metallic 294
Nausea 217, 218, 278, 388
Neurodegenerative diseases 33, 57, 58
Neurological disorders 57
NK cell cytotoxic activity 100
NLRP3 inflammasome 52
Nuclear magnetic resonance (NMR) 182

O

Oil 224, 249, 289, 293, 300, 307
 castor 300
 lavender 289
 olive 224, 293
 orange 289
 rosemary 289
 seed 249
 thyme 289, 307
Otosclerosis 209

P

Pain 59, 61, 96, 136, 278, 388
 abdominal 61, 278, 388
 chest 96
Peptides, antigenic 15, 93
Phagocytic assay 142, 147
Phagocytosis 10, 11, 12, 13, 14, 24, 25, 96,
 98, 99, 101, 198, 199, 382, 383
Pharmaceutical affairs 348, 358
 act 348
 law (PAL) 358
Plant-derived 166, 247, 378
 biochemicals 247
 immunomodulators 166, 378
Plant materials, medicinal 117

Platelet-activating factor (PAF) 206, 207
Pneumocystis 246
Pneumonia 31, 95, 96, 97, 246, 257, 404
Pneumonitis 218
Polycystic ovary syndrome (POS) 376
Polyendocrinopathy, autoimmune 45
Polygenic autoinflammatory diseases 64
Prostatic acid phosphatase (PAP) 68
Protease inhibitory activity 169
Proteins 221, 224
 metastasis 221
 metastatic 224

R

Reactive oxygen species (ROS) 66, 96, 101,
 171, 191, 201, 218, 228, 256, 374, 382
Renal disease 63
Respiratory 31, 98, 99, 138, 253, 257
 syncytial virus (RSV) 31, 98, 138, 253, 257
 tract infections 99
Reversed 135, 142, 144, 205
 passive Arthus reaction 205
 phase HPLC 132, 142, 144
Rhinitis 22, 49
 chronic 49
RhoA-dependent phosphorylation 63
Ribosome-inactivating protein (RIP) 149
RNA 101, 389
 dependent RNA polymerase enzyme 101
 synthesis 101
 therapies 389
Roifman syndrome 44

S

SDS-PAGE gel 150
Secondary 47, 48, 115, 146, 217, 219, 229,
 230, 402
 immunodeficiency disorders 47, 48
 metabolites 115, 146, 217, 219, 229, 230,
 402
Secretion, inflammatory proteins 12

Severe combined immune deficiency (SCID)
 43
Solid lipid nanoparticles (SLNs) 291, 292, 293
Splenectomy 48, 55
Stevens-Johnson syndrome (SJS) 27, 52, 53
Symptoms 78, 212
 hormone-dependent disease 78
 neuropsychiatric 212
Syndrome 44, 45, 46, 47, 48, 61, 62, 127, 376
 nephrotic 47, 48, 127
 polycystic ovary 376
Synovitis, symmetrical 210
Synthetic 41, 48, 60, 167, 176, 203, 209, 211,
 245, 258, 384, 386
 corticosteroids 386
 estrogen 176
 immunostimulator 384
 autoinflammatory diseases 60
 auto-inflammatory disorders (SAIDs) 41,
 60
 lupus erythematosus (SLE) 48, 167, 203,
 209, 211, 245, 258
 sclerosis 209

T

Techniques 179, 201, 209
 colorimetric Griess reaction assay 201
 immunopharmacological 209
 spectroscopic 179
Testing 193, 195
 immunomodulatory activity 193
 of immunological factors 195
Therapies, medicinal plant 110
Thin layer chromatography (TLC) 115, 118,
 158, 180, 204, 354
Thrombocytopenia, congenital 44
Thyroidectomy 57
Thyroid gland transplantation 57
Thyroiditis 56
Thyropoxidase 208
Traditional 77, 109, 111, 165, 171, 181, 218,
 258

Subject Index

Chinese medicine (TCM) 77, 109, 111,
165, 171, 218, 258
electrophoresis 181
Indian medicine 178
Traditional herbal 338, 344
 medicinal product (THMP) 338, 344
 remedies 338
Transcription factors 221
Tumour 14, 24, 51, 53, 59, 65, 95, 100, 200,
202, 218, 229, 232,
 destruction 218, 232
 heterogeneity 232
 microenvironment 229, 232
 necrosis factor (TNF) 14, 24, 51, 53, 59,
65, 95, 100, 200, 202
Type IV hypersensitivity reaction 26

U

Ulcers 61, 64, 144, 209
 genital 64
 oral 61
 peptic 144, 209

V

Vascular endothelial growth factor (VEGF)
176, 228, 230
Vomiting 278, 388

W

Wagner's reagent 155
Wiskott-Aldrich syndrome protein (WASP)
63

Z

Zika viruses 257
Zinc deficiency 30

