

Leishmaniasis

Biology, Control and
New Approaches for Its Treatment



Saurabh Bhatia

AAP | APPLE
ACADEMIC
PRESS

CRC CRC Press
Taylor & Francis Group

Leishmaniasis

Biology, Control, and New Approaches for Its Treatment

Saurabh Bhatia



Leishmaniasis: Biology, Control, and New Approaches for Its Treatment

Saurabh Bhatia

Apple Academic Press Inc.	Apple Academic Press Inc.
3333 Mistwell Crescent	9 Spinnaker Way
Oakville, ON L6L 0A2	Waretown, NJ 08758
Canada	USA

© 2016 by Apple Academic Press, Inc.

Exclusive worldwide distribution by CRC Press, a member of Taylor & Francis Group

No claim to original U.S. Government works

Printed in the United States of America on acid-free paper

International Standard Book Number-13: TK (Hardcover)

All rights reserved. No part of this work may be reprinted or reproduced or utilized in any form or by any electric, mechanical or other means, now known or hereafter invented, including photocopying and re-cording, or in any information storage or retrieval system, without permission in writing from the publisher or its distributor, except in the case of brief excerpts or quotations for use in reviews or critical articles.

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission and sources are indicated. Copyright for individual articles remains with the authors as indicated. A wide variety of references are listed. Reasonable efforts have been made to publish reliable data and information, but the authors, editors, and the publisher cannot assume responsibility for the validity of all materials or the consequences of their use. The authors, editors, and the publisher have attempted to trace the copyright holders of all material reproduced in this publication and apologize to copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged, please write and let us know so we may rectify in any future reprint.

Library and Archives Canada Cataloguing in Publication
TK

Library of Congress Cataloging-in-Publication Data
TK

Apple Academic Press also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic format. For information about Apple Academic Press products, visit our website at www.appleacademicpress.com and the CRC Press website at www.crcpress.com

CONTENTS

Preface

Chapter 1: Ayurveda and Leishmaniasis

- 1.1 Introduction to Ayurveda
- 1.2 Medicinal Plants in Ayurveda
- 1.3 Ayurvedic Classification of Plant-Based Drugs
- 1.4 Different Types of Ayurvedic Dosage
- 1.5 Extraction Procedures Used to Prepare These Preparations
- 1.6 Natural Therapies Used to Treat Disease
- 1.7 Formulas and Various Dosage Forms
- 1.8 Natural Remedies for Leishmaniasis
- 1.9 References

Chapter 2: Pharmacology of Leishmaniasis

- 2.1 Introduction
- 2.2 Etiology
- 2.3 Molecular Epidemiology
- 2.4 Transmission
- 2.5 Glycobiology of *Leishmania donovani*
- 2.6 Sand Fly-Leishmania Interactions
- 2.7 Leishmania-Macrophage Interactions
- 2.8 Antimicrobial Peptides with *Leishmania* and Their Functional Role in Host Parasitism
- 2.9 Biochemical Targets for Therapy
- 2.10 Drug Delivery Systems for Leishmaniasis
 - 2.10.1 Phagocytosis and Potential Drug Delivery System
- 2.11 Current Therapies
 - 2.11.1 Drugs in Clinical Development
 - 2.11.2 *Leishmania* Vaccines
 - 2.11.3 Adjuvant for *Leishmania* Vaccine
 - 2.11.4 Clinical Manifestations
 - 2.11.5 Visceral Leishmaniasis and Amphoterecin B
- 2.12 References

Chapter 3: Diagnosis and Strategies to Control Leishmaniasis

- 3.1 Diagnosis of Leishmaniasis
- 3.2 Various Identification and Culturing Practices Used During the Diagnosis of Leishmaniasis
- 3.3 Strategies to Control the Vector in Leishmaniasis
- 3.4 References

Chapter 4: Immunomodulatory Agents for Leishmaniasis

- 4.1 Introduction
- 4.2 Targeting of Host Immunity by Anti-Leishmanial Drugs
 - 4.2.1 Role of Neutrophils
 - 4.2.2 Monocytes and Macrophages
 - 4.2.3 Role of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)
 - 4.2.4 Role of DCS
 - 4.2.5 Lymphocytes
 - 4.2.6 Macrophage Derived Cytokines as a Measure of Immunomodulatory Activity
 - 4.2.7 Effect on Co-Stimulatory Molecules
- 4.3 Modulation of Signaling Events in Leishmania Infection
 - 4.3.1 Effect on Expression of CD40 and MAPK Signaling Pathways
 - 4.3.2 Toll-Like Receptors and Their Responsiveness in Leishmania Infection
 - 4.3.3 Leishmania Infection and Effect on JAK-STAT Pathways
 - 4.3.4 Modulation of NF- κ B Signaling Pathways by Leishmania
 - 4.3.5 Alterations of Host Cell Kinases and Phosphatases by Leishmania
- 4.4. References

Chapter 5: Ayurvedic Treatments for Leishmaniasis

- 5.1 Ayurvedia and Leishmania
- 5.2 Ayurvedic Prescriptions for Leishmaniasis
- 5.3 Ayurvedic Formulations Suitable for Leishmaniasis
- 5.4 Prevention
- 5.5 Possible Mechanisms
- 5.6 Ayurvedic Herbs for Leishmaniasis
- 5.7 Unani Treatment

Chapter 6: Phytotherapy for Leishmaniasis

- 6.1 Introduction
- 6.2 Natural Plant Products
 - 6.2.1 Mechanisms of Action of Plant-Derived Compounds
 - 6.2.1.1 Flavonoids
 - 6.2.1.2 Quinones
 - 6.2.1.3 Alkaloids
 - 6.2.1.4 Lignans
 - 6.2.1.5 Tannins
 - 6.2.1.6 Terpenoids
 - 6.2.1.7 Oxylipin
 - 6.2.1.7 Miscellaneous
- 6.3 Marine Sources
- 6.4 Miscellaneous Sources
- 6.5 References

Chapter 7: Elements Supplementation in Leishmaniasis

- 7.1 Introduction
- 7.2 Iron (Lauha Kalpas)
- 7.3 Zinc (Yasada, Rasaka or Kharpara)
- 7.4 Copper
- 7.5 Potassium
- 7.6 Magnesium
- 7.7 Calcium
- 7.8 Antimony and Arsenic
- 7.9 Mercury
- 7.10 Selenium
- 7.11 Vitamin C
- 7.12 References

Chapter 8: Alternative Therapies for Leishmaniasis

- 8.1 Introduction
- 8.2 Chelation Therapy
- 8.3 Oil Therapy
- 8.4 Acupuncture
- 8.5 References

Chapter 9: Inflammation and Leishmaniasis

- 9.1 Introduction
- 9.2 Evidence Acquisition
- 9.3 Description of the Database of Anti-Inflammatory Plants
- 9.4 Mechanism of Action of Natural Drugs
- 9.5 Ayurveda for Pain and Inflammation Management
- 9.6 Role of Anti-Inflammatory Plants in Leishmania
- 9.7 References

Chapter 10: Modern Treatment for Leishmaniasis

- 10.1 Introduction
- 10.2 Current Scenario on Leishmaniasis
 - 10.2.1 Protozoal Parasitic Disease: Current Situation and New Perspective
 - 10.2.2 The Leishmaniasis: A Global Problem
 - 10.2.2.1 Leishmaniasis: An Overview and Geographical Distribution
 - 10.2.2.2 Co-Infection of Leishmaniasis with AIDS
 - 10.2.2.3 Kala-Azar: History and Clinical Perspective
 - 10.2.2.4 Different Geographical Forms of Kala–Azar (KA)
 - 10.2.3 Protozoology of the Genus Leishmania
 - 10.2.3.1 Classification of the Genus Leishmania
 - 10.2.3.2 Morphology and Ultra-Structure of Leishmania
 - 10.2.3.3 Life Cycle of Leishmania
 - 10.2.3.4 Different Geographical Forms of Kala–Azar (KA)
 - 10.2.4 Epidemiology of Leishmaniasis
 - 10.2.4.1 Zoonotic Form versus Anthroponotic Form

- 10.2.4.2 Visceral Form versus Cutaneous Form
- 10.2.4.3 Acute Form versus Chronic Form
- 10.2.5. Transmission and Vectors
 - 10.2.5.1 Sandfly Transmission
 - 10.2.5.2 Congenital Transmission
 - 10.2.5.3 Blood Transfusion
 - 10.2.5.4 Direct Contact
- 10.2.6 Biochemistry of Leishmania
 - 10.2.6.1 Morphological Transformation of Leishmania
 - 10.2.6.2 Cultural Requirement
 - 10.2.6.3 Utilization of Substrates
 - 10.2.6.4 Energy Metabolism
- 10.2.7 Drugs Available for Treatment of Leishmaniasis
- 10.2.8 Outline of Promastigote and Amastigote Metabolism
- 10.2.9 An Overview of *L. donovani amastigote*
- 10.3 Review on Transplasma Membrane Electron Transport System
 - 10.3.1 Introduction
 - 10.3.2 The Evidence for Transplasma Membrane Electron Transport
 - 10.3.3 The Properties of Animal Cell Transmembrane Electron Transport
 - 10.3.4 Components of the Transplasma Membrane Electron Transport System
 - 10.3.5 Evidence for Co-Enzyme Q Function
 - 10.3.6 Inhibitors of Transplasma Membrane Electron Transport
 - 10.3.7. Proton Release Associated with Transplasma Membrane Electron Transport: Animal Cells
 - 10.3.8 Inhibition of Proton Release
 - 10.3.9. Mechanism of Electron Transport Driven Antiport
- 10.4. Electron Transport Chain

Index

ABOUT THE AUTHOR

Saurabh Bhatia, PhD, is currently an Assistant Professor at the PDM College of Pharmacy in Bahadurgarh, Haryana, India. He has several years of academic experience, teaching such specialized subjects as pharmacognosy, traditional concepts of medicinal plants, plant tissue culture, modern extraction and isolation methodologies, natural polymers, parasitology (*Leishmania*), medicinal and pharmaceutical values of marine and fresh water algae, and nanoparticles and peptide mediated drug delivery systems. He has promoted several marine algae and their derived polymers throughout India. He has written more than



30 international publications in these areas and has been an active participant of more than 35 national and international conferences. His published books include *Modern Applications of Plant Biotechnology in Pharmaceutical Science* and *Practical Applications of Plant Biotechnology* (in press).

Dr. Bhatia received his PhD from Jadhavpur University, Kolkata, India, and his MPharm from Bharati Vidyapeeth University in Pune, India.

PREFACE

Diseases caused by insect-borne trypanosomatid parasites are significant yet remain a neglected public health problem. *Leishmania*, a genus of unicellular protozoan parasite, is the causative organism of Leishmaniasis and is transmitted by female Phlebotomine sandflies, affecting millions of people worldwide. Infections caused by genus *Leishmania* is a major health problem worldwide, with high endemicity in developing countries. The disease currently threatens about 350 million women, men, and children in 88 countries around the world, with about two million affected annually. Using an overall case-fatality rate of 10%, a tentative estimate of 20,000 to 40,000 leishmanial deaths per year. Leishmaniasis is one of the most important parasitic infections, but current treatments are unsatisfactory due to their toxicity, cost, and resistance. Therefore, the development of new anti-leishmanial compounds is imperative. In the absence of a vaccine and in the wake of resistance to pentavalent antimonial drugs, there is an urgent need for effective drugs to replace/supplement those in current use.

Here in this book we are introducing various natural remedies to prevent or cure leishmaniasis. In addition to current pharmacological status, including etiology, molecular epidemiology, steps involved in transmission, including sand fly—*Leishmania* and *leishmania*—macrophage interactions, glycobiology and genetics of *Leishmania donovani*, new biochemical targets for therapy in contrast with MOA of recent chemotherapeutic agents, vaccines, and adjuvants for vaccine candidates, drug resistance, pathophysiology with clinical manifestations and development in diagnostic procedures, are also discussed. However the primary projection of the book is towards the treatment of leishmaniasis. The plant kingdom is undoubtedly valuable as a source of new medicinal agents. A series of ethnopharmacological surveys and reports suggest the traditional use of plants against different pathologies, and, interestingly, some of them presented anti-leishmanial activity in vitro and in vivo, possibly due to their immunostimulatory, healing, and microbicidal properties. Therefore the selection of a single or multiple plants against the *Leishmania* parasite can prove to be a successful approach to obtain new anti-leishmanial alternatives. The plant kingdom has in the past provided several affordable compounds, and therefore our book's main aim is to provide an overview of the current status of available leishmanicidal plant derived compounds that are effective singly or in combination with conventional anti-leishmanial drugs, yet are nontoxic to mammalian host cells. In addition this book also discusses reports of the anti-leishmanial products that are obtained from marine, fresh water, bacterial, fungal, and animal sources. Furthermore alternative therapies—such as the role of traditional systems (Ayurveda, Sidha, Unani and Tibi recommendations and oth-

er prescriptions suitable for leishmaniasis), homeopathy, dietary supplementation (especially metals and vitamins intake), chelation therapy, oil therapy, acupuncture and naturopathy—are comprehensively discussed. In addition to current a pharmacological update of leishmaniasis, this book covers the vast literature on natural extracts, isolated compounds, and alternative natural therapies to combat against *Leishmania* parasite.

There is dire need to have a book on therapy for leishmaniasis that is especially focused on the natural treatments and precautions adopted to treat and prevent leishmaniasis. Students always feel the unavailability of books on this topic, hence this attempt to fill the void of such necessity.

In addition to its focus on natural remedies, this book deals with comprehensive pharmacology and the current chemotherapeutic agents used against leishmaniasis. I am sure this book will serve as an important primer for students, researchers, and teachers who wish to learn traditional concepts to treat leishmaniasis in a simple way. It is my hope that this book will prove useful for all undergraduate, graduate, postgraduate students, researchers, and industrialists. We wrote this book of natural remedies for leishmaniasis primarily to share the available up-to-date knowledge with students, professors, researchers, and industrialists.

This book has fourteen chapters. All the chapters are written in a lucid way with necessary illustrations and up-to date-information so that students can become familiar with the relationship between holistic concepts and modern therapies for leishmaniasis. Errors and inaccuracies, if any, will be corrected through feedback and suggestion from readers. We earnestly believe that the book will be a valuable resource for undergraduate and postgraduate students.

The Publisher and President of Apple Academic Press, Ashish Kumar, must be praised for his active work and support in our effort. We are sure that readers of this book—students, researchers, and industrialists—will find it interesting and useful. The publication of this book would not have been possible without the valuable work of earlier researchers. This book would not have seen the light of the day without the moral support and patience of my parents. I am highly thankful to my parents and my dearest brother, Sanjay Bhatia, for his valuable suggestions and timely inputs. I am thankful to the PDM College of Pharmacy for providing me with a platform to work day and night on this book.

—Saurabh Bhatia, PhD

Leishmaniasis

Biology, Control and New Approaches for Its Treatment

Infections caused by *Leishmania* parasites, which are spread by the bite of phlebotomine sand flies, are a major worldwide health problem, with high endemicity in developing countries and causing significant morbidity and mortality in Africa, Asia, and Latin America. The resulting disease, leishmaniasis, currently threatens about 350 million women, men, and children in 88 countries around the world, with about 2 million affected annually.

The plant kingdom is undoubtedly a valuable and promising source of new medicinal agents to treat this endemic disease. This new volume provides exhaustive knowledge on a wide range of natural products and holistic concepts that have proved promising in the treatment of leishmaniasis. Including the major natural therapies as well as traditional formulations, over 300 medicinal plants and 150 isolated compounds that are reported to have beneficial results in the treatment of leishmaniasis are explored in this comprehensive book. In addition, this book also acts as an important resource on various anti-inflammatory plants that can be used to treatment various inflammatory conditions of the disease.

The potent leishmanicidal activities of certain chemically defined molecules isolated from natural origins are extensively discussed, and the pharmacology of leishmaniasis, including the latest updates on target sites and exploration of novel mechanisms of natural products against the *Leishmania* parasite are also included.

This new volume will prove invaluable for all scientists, researchers, practitioners, and others concerned with this life-threatening disease prevalent on several continents and which is now making its way out of poverty and into the United States.

About the Author

Saurabh Bhatia, PhD, is currently an Assistant Professor at the PDM College of Pharmacy in Bahadurgarh, Haryana, India. He has several years of academic experience, teaching such specialized subjects as pharmacognosy, traditional concepts of medicinal plants, plant tissue culture, modern extraction and isolation methodologies, natural polymers, parasitology (*Leishmania*), medicinal and pharmaceutical values of marine and fresh water algae, and nanoparticles and peptide mediated drug delivery systems. He has written more than 30 international publications in these areas and has been an active participant of more than 35 national and international conferences. His published books include *Modern Applications of Plant Biotechnology in Pharmaceutical Science* and *Practical Applications of Plant Biotechnology (in press)*.

AAP | APPLE
ACADEMIC
PRESS

www.appleacademicpress.com

