SpringerBriefs in Pharmaceutical Science & Drug Development

For further volumes:
<http://www.springer.com/series/10224>

Gabriela Hrcakova · Samuel Velebny

Pharmacological Potential of Selected Natural Compounds in the Control of Parasitic Diseases

Gabriela Hrcakova
Slovak Academy of Sciences
Institute of Parasitology
Kosice
Slovakia

Samuel Velebny
Slovak Academy of Sciences
Institute of Parasitology
Kosice
Slovakia

ISSN 1864-8118
ISBN 978-3-7091-1324-0
DOI 10.1007/978-3-7091-1325-7
Springer Wien Heidelberg New York Dordrecht London

ISSN 1864-8126 (electronic)
ISBN 978-3-7091-1325-7 (eBook)

Library of Congress Control Number: 2012952683

© The Author(s) 2013

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface

The disease burden caused by parasitic protozoa and worms is significant and represents a challenging health problem mainly in tropics. The drugs currently used for the treatment of parasitic infections are mostly effective, however, some of them have limitations, such as toxic side effects and high cost. Moreover, some parasitic organisms developed resistance to many of these drugs. There is a need for discovery of new drugs. For centuries, medicinal plants have been used to combat parasitism, and in many parts of the world are still used for this purpose. Plants are valuable sources for the screening of bioactive secondary metabolites, but also bacteria, fungi, terrestrial and marine invertebrates produce pharmaceutically useful compounds with potential antiparasitic activity. Natural product research shows promise in finding new lead structures besides rational drug design.

The search for bioactive natural molecules begins with the screening of various extracts, isolation of active fractions, and identification of the active components when possible. This search must consider, among other things, target specificity, making better use of the biochemical and biological characteristics of individual parasite species, and cytotoxicity determination. This is a multidisciplinary process, which is initially realized in vitro, however, therapeutic concepts have to be validated and toxicity of selected compounds evaluated in animal studies.

Malaria, trypanosomiasis, and leishmaniasis are among the most important public health problems in developing countries. [Chapter 1](#) reviews the most promising results obtained during the screening of antimalarial, trypanocidal, and leishmanicidal properties of natural products classified according to their chemical structure since the year 2000.

[Chapter 2](#) is devoted to the review of anthelmintic properties of bioactive compounds isolated from the various natural sources. Particular attention is paid to the mode of anthelmintic action of natural alkaloids, essential oils, flavonoids, glycosides, saponins, condensed tannins, endoperoxide sesquiterpene lactones, enzymes, and amides against many species of round and flatworms.

How do the natural compounds exert their anthelmintic effects? To get the answers to this question, many examples are presented from the point of view

of benefits for the host (antioxidant and immunomodulatory effects) and direct anthelmintic action of screened compounds in [Chap. 3](#).

It is our hope that this book will provide the readers with a useful survey of the recent results in the screening of natural compounds with promising antimalarial, trypanocidal, leishmanicidal, but mainly anthelmintic effects and that it may serve as a valuable source of information for scientists, postgraduate and graduate students working in medical and pharmacological research.

Acknowledgments

We would like to express our deep gratitude to Prof. Chris Arme (Keele University, United Kingdom) for his essential help in the manuscript preparation. We also thank for financial support to the Scientific Grant Agency of the Ministry of Education of the Slovak Republic - VEGA, under contract Nos. 2/7188/27 and 2/0188/10.

Contents

1	Pharmacological Potential of Natural Compounds in the Control of Selected Protozoan Diseases	1
1.1	The Most Serious Protozoan Infections: Pathology, Therapy, and Drug Resistance	1
1.2	Bioactive Natural Compounds: Their Chemical Classification and Evaluation of Biological Activity Against <i>Plasmodium</i> , <i>Trypanosoma</i> , and <i>Leishmania</i>	7
1.3	Natural Antimalarials	9
1.3.1	Antimalarials Isolated from Higher Plants	9
1.3.2	Antiplasmodials Isolated from Bacteria, Fungi and Marine Organisms	13
1.4	Natural Antitrypanosomals	15
1.4.1	Antitrypanosomals Isolated from Higher Plants	15
1.4.2	Antitrypanosomals Isolated from Bacteria, Fungi and Marine Organisms	18
1.5	Natural Antileishmanials	19
1.5.1	Antileishmanials Isolated from Higher Plants	19
1.5.2	Antileishmanials Isolated from Bacteria, Fungi and Marine Organisms	23
1.6	Conclusion	23
	References	23
2	Parasitic Helminths of Humans and Animals: Health Impact and Control	29
2.1	Anthelmintic Drugs: Mode of Action, Efficacy and Resistance	29
2.2	Natural Compounds from Lower Terrestrial and Marine Organisms in Anthelmintic Drug Discovery	33

2.3	Anthelmintic Potential of Higher Plants	38
2.3.1	Plant Extracts	39
2.3.2	Alkaloids	51
2.3.3	Essential Oils	54
2.3.4	Flavonoids and Polyphenols	61
2.3.5	Glycosides and Saponins	66
2.3.6	Enzymes, Amides and Other Specific Compounds	69
2.3.7	Condensed Tannins and Sesquiterpene Lactones	71
2.3.8	Endoperoxide Sesquiterpene Lactone Artemisinin and Derivates	75
2.4	Concluding Remarks	81
	References	83
3	Natural Compounds Exerting Anthelmintic and/or Host-Protecting Effects During Parasitic Infections	101
3.1	Host Pathology and Immunosuppression During Helminth Infections	102
3.2	Compounds Affecting Parasites and Mammalian Hosts: Anthelmintic Action Versus Benefit for Hosts.	104
3.3	Natural Compounds with Antioxidant and Immunomodulatory Effects: Synergism with Anthelmintic Drugs.	110
3.4	Concluding Remarks	117
3.5	Appendix	117
	References	120

Introduction

For thousands of years, natural products have played an important role throughout the world in treatment and prevention of various diseases in humans and animals. Natural product medicines have been collected from various sources, mostly terrestrial plants and microorganisms and marine organisms, and they have been the major source of chemical diversity for starting materials driving pharmaceutical discovery over the past century.

Infectious diseases caused by parasitic protozoan and metazoan species, in spite of an immense effort put into eradication programs within the past 20 years, are still on the list of the most frequently encountered diseases in tropical countries. The most debilitating protozoan diseases, including malaria, leishmaniasis, and trypanosomiasis, for millenia have prevented economic and cultural development in vast regions of the world and still are a major social, economical, and health problem today. Estimates show that approximately 300–500 million people are at risk from these infections. The World Health Organization estimates that approximately 2 billion people harbor parasitic worm infections, and worm infections in livestock are an important factor affecting food production.

Before commercial anthelmintics were introduced into the world market, worm infections were controlled using specific plants, which, based more on belief rather than on sound knowledge, were credited with having specific actions. Plants with antiparasitic properties could be found in temperate, tropical as well as colder climates in the world; however, the highest diversity of plants with ethnomedicinal or ethnoveterinary records can be found in tropical regions. Nowadays, therapy and prevention of parasitic infections is facing several major issues: emergence and rapid spread of resistant strains of parasites and the limited number of safe and highly effective antiparasitic drugs, which in turn leads to monotherapy of a particular disease.

The frequent use of a few alternative drugs, together with other biological factors, contributed to the development of multidrug resistant malaria strains with no alternative treatment possibilities. There are only a few classes of anthelmintic drugs for therapy and prevention of so-called neglected tropical diseases

of humans caused by metazoan parasites, and drug resistance has been reported already from some endemic regions. Anthelmintic resistance of gastrointestinal nematodes in small ruminants, which are bred for the production of meat, milk, or wool, is a global problem that leads to enormous economic losses. In this context, the administration of combinations of either two anthelmintics or co-administration of drugs, with natural compounds with a similar spectrum of activity and different mechanisms of action, has been suggested as a potential means of delaying the development of drug resistance.

The very high cost of discovering and developing new drugs has led to the introduction of only a few new products in the market displaying a new mode of action within the past 20 years. To identify new antiparasitic lead compounds, large numbers of compounds will have to be examined in pre-clinical tests. They come mostly from the laboratories of medical chemists, but highly successful sources of compounds can also be found in nature. Higher plants, but also symbionts like lichens, are able to synthesize the specific compounds identified as secondary metabolites. As the term implies, they are not strictly essential to the main functions of the plants, such as their growth and reproduction. They have been associated, for example, with plant defence mechanisms against pathogens, but other functions have also been described. Plant-derived secondary metabolites can be divided, on the basis of their molecular formulae and structural motifs, into several classes and the most abundant are essential oils, flavonoids, alkaloids, saponins, glycosides, tannins, sesquiterpene lactones, lactones with peroxidic structure, amides, and proteins with enzymatic activity.

The WHO has recognized the importance of traditional medicine since the late 1970s, when its Traditional Medicine Programme was established. It has developed guidelines for the assessment of herbal medicines focussing mainly on malaria and other important protozoan infections. Similar programs have been initiated since the 1980s to discover novel lead molecules against filarial nematodes, human trematodiasis, and gastrointestinal nematodes of livestock. Isolation of artemisinins from the plant *Artemisia annua* and avermectins from the terrestrial actinomycete, *Streptomyces avermectinius*, within the 1970s are probably two major successes of intensive screening program of compounds from natural sources. The world's ocean is extremely rich in living organisms, of which marine invertebrates comprise a diverse and promising source of compounds from a wide variety of structural classes. Marine-derived small molecules have been described from marine plants, animals, algae, fungi, and bacteria, etc. Many of them are chemically unique compounds and many have been successfully isolated and characterized, and synthetic derivatives have been subjected to a large-scale screening against protozoan parasites.

Since 2000, the interest in evaluation of biological, medicinal, and antiparasitic activities of natural compounds has increased considerably, as indicated by the high number of published scientific papers. After reviewing numerous papers, we noticed that a very high number of small compounds from natural sources were evaluated for their cytotoxic activity against three major human protozoan infections, with a large proportion of molecules being derived from marine

organisms. On the other hand, antiparasitic effects against trematodes, cestodes, and nematodes were attributed mostly to either the whole plant extracts or to a whole group of secondary metabolites, like tannins or essential oils. Lower numbers, and mostly very recent studies, involved chemically defined, and either purified or chemically synthesized, natural compounds using a variety of experimental helminth infections. Therefore the main purpose of this book was to draw attention to the wide variety of compounds from various natural sources, so far evaluated for antiparasitic activity. We also aimed to bring an overview of their potential not only against major protozoan infections of humans, but also against the most pathogenic helminth parasites together with the possible mechanism of action, cytotoxicity, or side effects on hosts. We hope that this comprehensive overview will illustrate the complexity of this issue for those interested in pharmacological research in the field of parasitology.