ANNUAL PLANT REVIEWS VOLUME 39

Functions and Biotechnology of Plant Secondary Metabolites, Second edition Edited by Michael Wink
 ISBN: 978-1-405-18528-8

ANNUAL PLANT REVIEWS VOLUME 39

Functions and Biotechnology of Plant Secondary Metabolites

Second edition

Edited by

Michael Wink

Professor of Pharmaceutical Biology
Institute of Pharmacy and Molecular Biotechnology
Heidelberg University
Germany

WILEY-BLACKWELL

A John Wiley & Sons, Ltd., Publication

Annual Plant Reviews

This edition first published 2010

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing programme has been merged with Wiley's global Scientific, Technical and Medical business to form Willey-Blackwell.

Registered office
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

Editorial offices
9600 Garsington Road, Oxford, OX4 2DQ, United Kingdom
2121 State Avenue, Ames, Iowa 50014-8300, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell.

Library of Congress Cataloging-in-Publication Data

Functions and biotechnology of plant secondary metabolites / edited by
Michael Wink. – 2nd ed.
p. cm. – (Annual plant reviews ; v. 39)
Rev. ed. of: Functions of plant secondary metabolites and their exploitation in biotechnology.
Includes bibliographical references and index.
ISBN 978-1-4051-8528-8 (hardback : alk. paper)
1. Plant metabolites. 2. Metabolism, Secondary. 3. Plant biotechnology.
I. Wink, Michael. II. Functions of plant secondary metabolites and their exploitation in biotechnology. III. Series: Annual plant reviews ; v. 39.
QK887.F86 2010
572'.42–dc22

2009031828

A catalogue record for this book is available from the British Library.

Set in 10/12 pt Palatino by Aptara® Inc., New Delhi, India
Printed in Singapore

1 2010

Annual Plant Reviews
A series for researchers and postgraduates in the plant sciences. Each volume in this series focuses on a theme of topical importance and emphasis is placed on rapid publication.

Titles in the series:
1. **Arabidopsis**
   Edited by M. Anderson and J.A. Roberts
2. **Biochemistry of Plant Secondary Metabolism**
   Edited by M. Wink
3. **Functions of Plant Secondary Metabolites and their Exploitation in Biotechnology**
   Edited by M. Wink
4. **Molecular Plant Pathology**
   Edited by M. Dickinson and J. Beynon
5. **Vacuolar Compartments**
   Edited by D.G. Robinson and J.C. Rogers
6. **Plant Reproduction**
   Edited by S.D. O'Neill and J.A. Roberts
7. **Protein–Protein Interactions in Plant Biology**
   Edited by M.T. McManus, W.A. Laing and A.C. Allan
8. **The Plant CellWall**
   Edited by J.K.C. Rose
9. **The Golgi Apparatus and the Plant Secretory Pathway**
   Edited by D.G. Robinson
10. **The Plant Cytoskeleton in Cell Differentiation and Development**
    Edited by P.J. Hussey
11. **Plant–Pathogen Interactions**
    Edited by N.J. Talbot
12. **Polarity in Plants**
    Edited by K. Lindsey
13. **Plastids**
    Edited by S.G. Moller
14. **Plant Pigments and their Manipulation**
    Edited by K.M. Davies

15. **Membrane Transport in Plants**
    Edited by M.R. Blatt
16. **Intercellular Communication in Plants**
    Edited by A.J. Fleming
17. **Plant Architecture and Its Manipulation**
    Edited by CGN Turnbull
18. **Plasmodeomata**
    Edited by K.J. Oparka
19. **Plant Epigenetics**
    Edited by P. Meyer
20. **Flowering and Its Manipulation**
    Edited by C. Ainsworth
21. **Endogenous Plant Rhythms**
    Edited by A. Hall and H. McWatters
22. **Control of Primary Metabolism in Plants**
    Edited by W.C. Plaxton and M.T. McManus
23. **Biology of the Plant Cuticle**
    Edited by M. Riederer
24. **Plant Hormone Signaling**
    Edited by P. Hadden and S.G. Thomas
25. **Plant Cell Separation and Adhesion**
    Edited by J.R. Roberts and Z. Gonzalez-Carranza
26. **Senescence Processes in Plants**
    Edited by S. Gan
27. **Seed Development, Dormancy and Germination**
    Edited by K.J. Bradford and H. Nonogaki
28. **Plant Proteomics**
    Edited by C. Finnie
29. **Regulation of Transcription in Plants**
    Edited by K. Grasser
30. **Light and Plant Development**
    Edited by G. Whitelam
31. **Plant Mitochondria**
    Edited by David C. Logan
32. **Cell Cycle Control and Plant Development**
    Edited by D. Inzé
33. **Intracellular Signaling in Plants**
    Edited by Z. Yang
34. **Molecular Aspects of Plant Disease Resistance**
    Edited by Jane Parker
35. **Plant Systems Biology**
    Edited by Gloria M. Coruzzi and Rodrigo A. Gutiérrez
36. **The Moss *Physcomitrella patens***
    Edited by C.D. Knight, P.-F. Perroud and D.J. Cove
37. **Root Development**
    Edited by Tom Beeckman
38. **Fruit Development and Seed Dispersal**
    Edited by Lars Østergaard

CONTENTS

List of contributors ix
Preface xi

1 Introduction 1
Michael Wink

1.1 Ecological function of secondary metabolites 1
1.2 Presence of defence and signal compounds at the right time and place 4
1.3 Molecular modes of action of SM 8
1.4 Biotechnology and utilization of SM 13
1.5 Conclusions 16

2 Molecular Modes of Action of Defensive Secondary Metabolites 21
Michael Wink and Oskar Schimmer

2.1 Introduction 21
2.2 Molecular modes of action – an overview 22
2.3 Accumulation of defence and signal compounds in plants 128
2.4 Animal responses: detoxification mechanisms and adaptations 132
2.5 Concluding remarks 137

3 Chemical Defence in Marine Ecosystems 162
Annika Putz and Peter Proksch

3.1 Introduction 162
3.2 Marine natural products in allelopathic interactions 165
3.3 Chemical defence against fouling 168
3.4 Chemical defences of marine invertebrates and algae against consumers 173
3.5 Favoured allocation of defensive metabolites in vulnerable and valuable parts of marine invertebrates and algae 182
3.6 The flexible response: stress-induced accumulation of defence metabolites and activation of protoxins 186
3.7 Endosymbionts as sources for allelochemicals found in marine invertebrates 193
3.8 Conclusions and outlook 201

4 Plant–Microbe Interactions and Secondary Metabolites with Antibacterial, Antifungal and Antiviral Properties 214
Jürgen Reichling

4.1 Introduction 215
4.2 Phytoalexins 217
4.3 Antibacterial and antifungal agents of higher plants 232
4.4 Secondary metabolites from higher plants with antiviral properties 278
4.5 Conclusions 317

5 New Medical Applications of Plant Secondary Metabolites 348
Jörg Heilmann

5.1 Introduction 349
5.2 Compounds with anticancer and chemopreventive activity 349
5.3 Antiviral compounds 359
5.4 Antimalarial drugs 360
5.5 Anti-inflammatory drugs 361
5.6 Antidepressant drugs 363
5.7 Anti-ischaemic drugs 364
5.8 Immunostimulatory drugs 365
5.9 Conclusions 366

6 Production of Natural Products by Plant Cell and Organ Cultures 381
August-Wilhelm Alfermann

6.1 Introduction 381
6.2 Production of natural products by cell and organ cultures 383
6.3 Elicitation 383
6.4 Increase/decrease of product yields by genetic manipulation 384
6.5 Biosynthetic pathways delineation using RNA-interference 385
6.6 Mass cultivation of plant cell cultures 386
6.7 Production of recombinant proteins by plants and plant cell cultures 388
6.8 Production of plant natural products in microbes 389
6.9 Perspectives 390

Index 399
Colour plate (between pages 50 and 51)

CONTRIBUTORS

August-Wilhelm Alfermann
University of Düsseldorf
Institute of Molecular Biology of Plants
Universitätsstr. 1
40225 Düsseldorf
Germany

Jörg Heilmann
University of Regensburg
Faculty of Natural Sciences
Pharmaceutical Biology
93040 Regensburg
Germany

Peter Proksch
University of Düsseldorf
Institute of Pharmaceutical Biology and Biotechnology
Universitätsstr. 1
40225 Düsseldorf
Germany

Annika Putz
University of Düsseldorf
Institute of Pharmaceutical Biology and Biotechnology
Universitätsstr. 1
40225 Düsseldorf
Germany

Jürgen Reichling
Ruprecht-Karls-University Heidelberg
Institute of Pharmacy and Molecular Biotechnology
Div. Biology
Im Neuenheimer Feld 364
69120 Heidelberg
Germany

Oskar Schimmer
Retired from
University Erlangen-Nürnberg
Institute of Botany and Pharmaceutical Biology
Erlangen
Germany

Michael Wink
Ruprecht-Karls-University Heidelberg
Institute of Pharmacy and Molecular Biotechnology
Div. Biology
Im Neuenheimer Feld 364
69120 Heidelberg
Germany

PREFACE

A characteristic feature of plants is their capacity to synthesize and store a wide variety of low-molecular-weight compounds, the so-called **secondary metabolites (SM)** or natural products. The number of described structures exceeds 100 000; the real number in nature is certainly much higher because only 20–30% of plants have been investigated in phytochemistry so far. In contrast to primary metabolites, which are essential for the life of every plant, the individual types of SM usually occur in a limited number of plants, indicating that they are not essential for primary metabolism, i.e. anabolism or catabolism.

Whereas SM had been considered to be waste products or otherwise useless compounds for many years, it has become evident over the last three decades that SM have important roles for the plants producing them: they may function as signal compounds within the plant, or between the plant, producing them and other plants, microbes, herbivores, predators of herbivores, pollinating or seed-dispersing animals. More often SM serve as defence chemicals against herbivorous animals (insects, molluscs, mammals), microbes (bacteria, fungi), viruses or plants competing for light, water and nutrients. Therefore, SM are ultimately important for the fitness of the plant producing them. Plants usually produce complex mixtures of SM, often representing different classes, such as alkaloids, phenolics or terpenoids. It is likely that the individual components of a mixture can exert not only additive but certainly also synergistic effects by attacking more than a single molecular target. Because the structures of SM have been shaped and optimised during more than 500 million years of evolution, many of them exert interesting biological and pharmacological properties which make them useful for medicine or as biorational pesticides.

In this volume of Annual Plant Reviews, we have tried to provide an up-to-date survey of the function of plant SM, their modes of action and their use in pharmacology as molecular probes, in medicine as therapeutic agents, and in agriculture as biorational pesticides. A companion volume – *Biochemistry of Plant Secondary Metabolism* edited by M. Wink – published simultaneously provides overviews of the biosynthetic pathways (enzymes, genes) leading to the formation of alkaloids, glucosinolates, cyanogenic glucosides, non-protein amino acids, flavonoids and other phenolics and terpenoids. The mechanisms of transport and storage were also discussed as well as a general outline of the evolution of secondary metabolism.

The present volume is the second edition of a successful first edition, which was published in 1999 and which has received many positive responses from its readers. To achieve a comprehensive and up-to-date summary, we have invited scientists who are specialists in their particular areas to update their previous chapters. The present volume draws together results from a broad area of biochemistry, pharmacology and pharmacy and it cannot be exhaustive on such a large and diverse group of substances. Emphasis was placed on new results and concepts which have emerged over the last decades.

The volume starts with a bird's eye view of the function and utilization of SM (M. Wink), followed by a more detailed overview over the various modes of action of SM (M. Wink and O. Schimmer), including interactions with the major molecular targets, such as biomembranes, proteins and DNA. Some emphasis is placed on DNA modifying metabolites, on mechanisms involved in cytotoxicity and on SM interfering with elements of neuronal signal transduction (neuroreceptors, ion channels). The production of SM for defence is not restricted to plants, but can also be seen in other sessile organisms. SM are especially abundant in marine organisms. A. Putz and P. Proksch explore chemical defence in marine ecosystems. Because plants have to defend themselves against bacteria, fungi and viruses, it is not surprising that many SM exert antibacterial, antifungal and antiviral properties. The antimicrobial properties are reviewed with a special emphasis on medical application (J. Reichling). Because many pathogens have become resistant against antibiotics (e.g. MRSA), antibiotic substances from plants with different modes of actions become more important in the future. Mankind has used medicinal plants for thousands of years to treat health disorders and diseases. Although many of the traditional applications have been replaced by synthetic drugs these days, phytomedicine and phytotherapy is still in use and receiving much attention. J. Heilmann reviews new findings of plant-derived drug in the context of anticancer and chemopreventive properties, and drugs with anti-inflammatory, antidepressant, anti-ischaemic, antimalarial and immunostimulatory activities. The final chapter addresses the problem of the production of SM as some of them are difficult to obtain and thus very costly. An alternative to the plantation of medicinal plants in the field is the production of SM in plant cell and organ cultures or by recombinant microorganisms. The recent results and developments are reviewed by W. Alfermann.

The book is designed for use by advanced students, researchers and professionals in plant biochemistry, physiology, molecular biology, genetics, agriculture and pharmacy working in the academic and industrial sectors, including the pesticide and pharmaceutical industries.

The book brought together contributions from friends and colleagues in many parts of the world. As editor, I thank all those who have taken part in writing and preparation of this book. I thank Theodor C. H. Cole for help in preparation of the index. Special thanks go to the project editor Catriona Dixon from Wiley-Blackwell and her team for their interest, support and encouragement.

Michael Wink
Heidelberg