

AGING

Oxidative Stress and Dietary Antioxidants

Edited by
VICTOR R. PREEDY

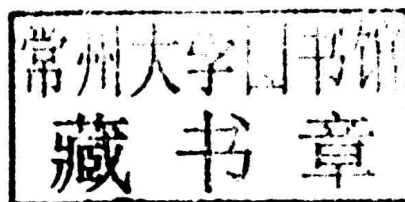


AGING: OXIDATIVE STRESS AND DIETARY ANTIOXIDANTS

Edited by

VICTOR R. PREEDY

*King's College London,
London, UK*



AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier



Academic Press is an imprint of Elsevier
The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK
225 Wyman Street, Waltham, MA 02451, USA

First published 2014

Copyright © 2014 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangement with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency can be found at our website: www.elsevier.com/permissions

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors assume any liability 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, instructions, or ideas contained in the material herein.

British Library Cataloguing in Publication Data

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

Library of Congress Cataloguing in Publication Data

A catalogue record for this book is available from the Library of Congress

ISBN: 978-0-12-405933-7

For information on all Academic Press publications
visit our website at store.elsevier.com

Printed and bound by CPI Group (UK) Ltd, Croydon, CR0 4YY

14 15 16 17 10 9 8 7 6 5 4 3 2 1

 ELSEVIER	 Book Aid International	Working together to grow libraries in developing countries
www.elsevier.com • www.bookaid.org		

AGING: OXIDATIVE STRESS AND DIETARY ANTIOXIDANTS

Contributors

- Shadwan Alsafwah** Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN, USA
- Fawaz Alzaid** Diabetes and Nutritional Sciences Division, School of Medicine, King's College London, Franklin-Wilkins Building, London, UK
- B. Andallu** Sri Sathya Sai Institute of Higher Learning, Anantapur, A.P., India
- Raza Askari** Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN, USA
- Sylvette Ayala-Peña** Department of Pharmacology and Toxicology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico
- Mario Barbagallo** Geriatric Unit, Department of Internal Medicine DIBIMIS, University of Palermo, Italy
- I.F.F. Benzie** Department of Health Technology & Informatics, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong
- Syamal K. Bhattacharya** Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN, USA
- Brunna Cristina Bremer Boaventura** Department of Nutrition, Health Sciences Center, Federal University of Santa Catarina, Campus Trindade, Florianópolis/SC, Brazil
- Corinne Caillaud** Exercise Physiology and Nutrition, Faculty of Health Sciences, University of Sydney, Lidcombe NSW, Australia
- Antonio Camargo** Lipids and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatología Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain
- José Eduardo de Aguiar-Nascimento** Department of Surgery, Julio Muller University Hospital, Federal University of Mato Grosso, Cuiaba, Mato Grosso, Brazil
- Javier Delgado-Lista** Lipids and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatología Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain
- Patricia Faria Di Pietro** Department of Nutrition, Health Sciences Center, Federal University of Santa Catarina, Campus Trindade, Florianópolis/SC, Brazil
- Dwight A. Dishmon** Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN, USA
- Ligia J. Dominguez** Geriatric Unit, Department of Internal Medicine DIBIMIS, University of Palermo, Italy
- Victor Farah** Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN, USA
- Antonio Garcia-Rios** Lipids and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatología Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain
- M. Garrido** Department of Physiology (Neuroimmunophysiology and Chrononutrition Research Group), Faculty of Science, University of Extremadura, Badajoz, Spain
- Jeffrey S. Greiwe** Ausio Pharmaceuticals, LLC, Cincinnati, Ohio, USA
- Erika Hosoi** Research Team for Promoting the Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
- Chao A. Hsiung** Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan
- Chih-Cheng Hsu** Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan
- Nikolay K. Isaev** Lomonosov Moscow State University, A.N. Belozersky Institute of Physico-Chemical Biology, Moscow, Russia
- Akihito Ishigami** Molecular Regulation of Aging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
- Hiroyasu Iso** Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
- Richard L. Jackson** Ausio Pharmaceuticals, LLC, Cincinnati, Ohio, USA
- N.N. Kang** Department of Nutritional Sciences, University of Toronto, Toronto, Canada
- Nadezhda A. Kapay** Department of Brain Research, Research Center of Neurology, Russian Academy of Medical Sciences, Pereulok Obukha 5, Moscow, Russia
- Jozef Kedziora** Department of Biochemistry, Collegium Medicum UMK in Bydgoszcz, Poland
- Kornelia Kedziora-Kornatowska** Department and Clinic of Geriatrics, Collegium Medicum UMK in Bydgoszcz, Poland
- Hirofumi Koyama** Department of Advanced Aging Medicine, Chiba University Graduate School of Medicine, Inohana, Chuo-ku, Chiba, Japan
- Xi-Zhang Lin** Department of Internal Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
- Xiaoyan Liu** University of Texas Health Science Center at San Antonio, Department of Cellular and Structural Biology, San Antonio, TX, USA, and The Preclinical Medicine Institute of Beijing, University of Chinese Medicine, Chao Yang District, Beijing, China

- Jose Lopez-Miranda** Lipids and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain
- Konstantin G. Lyamzaev** Lomonosov Moscow State University, A.N. Belozersky Institute of Physico-Chemical Biology, Moscow, Russia
- Lucien C. Manchester** University of Texas Health Science Center at San Antonio, Department of Cellular and Structural Biology, San Antonio, TX, USA
- Koutatsu Maruyama** Department of Basic Medical Research and Education, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan
- M.S. Mekha** Sri Sathya Sai Institute of Higher Learning, Anantapur, A.P., India
- Maria Grazia Modena** University of Modena and Reggio Emilia, Italy
- Suhaila Mohamed** Institute of BioScience, Universiti Putra Malaysia, Serdang, Selangor, Malaysia
- Daichi Morikawa** Department of Advanced Aging Medicine, Chiba University Graduate School of Medicine, Chuo-ku, Chiba, Japan, and Department of Orthopaedics, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan
- Hidetoshi Nojiri** Department of Orthopaedics, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan
- Vinood B. Patel** Department of Biomedical Science, Faculty of Science & Technology, University of Westminster, London, UK
- Francisco Perez-Jimenez** Lipids and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain
- Pablo Pérez-Martínez** Lipids and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain
- Olga V. Popova** Department of Brain Research, Research Center of Neurology, Russian Academy of Medical Sciences, Pereulok Obukha 5, Moscow, Russia
- Ananda S. Prasad** Department of Oncology, Wayne State University School of Medicine and Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA
- Victor R. Preedy** Diabetes and Nutritional Sciences Division, School of Medicine, King's College London, Franklin-Wilkins Building, London, UK
- C.U. Rajeshwari** Sri Sathya Sai Institute of Higher Learning, Anantapur, A.P., India
- A.V. Rao** Department of Nutritional Sciences, University of Toronto, Toronto, Canada
- L.G. Rao** Department of Medicine, St Michael's Hospital and University of Toronto, Toronto, Canada
- Russel J. Reiter** University of Texas Health Science Center at San Antonio, Department of Cellular and Structural Biology, San Antonio, TX, USA
- A.B. Rodríguez** Department of Physiology (Neuroimmunophysiology and Chrononutrition Research Group), Faculty of Science, University of Extremadura, Badajoz, Spain
- Sergio A. Rosales-Corral** Centro de Investigacion Biomedica de Occidente, Instituto Mexicano Del Seguro Social, Guadalajara, Jalisco, Mexico, and University of Texas Health Science Center at San Antonio, Department of Cellular and Structural Biology, San Antonio, TX, USA
- Joanna Rybka** Department of Biochemistry, Collegium Medicum UMK in Bydgoszcz, Poland, and Life4Science Foundation, Bydgoszcz, Poland
- Kyoko Saito** Research Team for Promoting the Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
- Dipayan Sarkar** Department of Plant Sciences, Loftsgard Hall, NDSU, Fargo, ND, USA
- Rahul Saxena** Department of Biochemistry, School of Medical Sciences & Research, Sharda University, Greater Noida (UP), India
- Irina N. Scharonova** Department of Brain Research, Research Center of Neurology, Russian Academy of Medical Sciences, Pereulok Obukha 5, Moscow, Russia
- Richard J. Schwen** Ausio Pharmaceuticals, LLC, Cincinnati, Ohio, USA
- Kalidas Shetty** Department of Plant Sciences, Loftsgard Hall, NDSU, Fargo, ND, USA
- Shuichi Shibuya** Department of Advanced Aging Medicine, Chiba University Graduate School of Medicine, Chuo-ku, Chiba, Japan
- Takahiko Shimizu** Department of Advanced Aging Medicine, Chiba University Graduate School of Medicine, Inohana, Chuo-ku, Chiba, Japan
- R.I. Shobha** Sri Sathya Sai Institute of Higher Learning, Anantapur, A.P., India
- David Simar** Inflammation and Infection Research, School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney NSW, Australia
- P.M. Siu** Department of Health Technology & Informatics, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong
- Vladimir G. Skrebitsky** Department of Brain Research, Research Center of Neurology, Russian Academy of Medical Sciences, Pereulok Obukha 5, Moscow, Russia
- Vladimir P. Skulachev** Lomonosov Moscow State University, A.N. Belozersky Institute of Physico-Chemical Biology, Moscow, Russia
- John M. Starr** Centre for Cognitive Ageing and Cognitive Epidemiology, Edinburgh, United Kingdom
- Robert J. Starr** School of Medicine and Dentistry, Polwarth Building, Foresterhill, Aberdeen, United Kingdom
- Elena V. Stelmashook** Department of Brain Research, Research Center of Neurology, Russian Academy of Medical Sciences, Pereulok Obukha 5, Moscow, Russia
- Dun-Xian Tan** University of Texas Health Science Center at San Antonio, Department of Cellular and Structural Biology, San Antonio, TX, USA

M.P. Terrón Department of Physiology (Neuroimmunophysiology and Chrononutrition Research Group), Faculty of Science, University of Extremadura, Badajoz, Spain

Carlos A. Torres-Ramos Department of Physiology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

Floor van Heesch Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, The Netherlands

S. Wachtel-Galor Department of Health Technology & Informatics, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

Karl T. Weber Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN, USA

I-Chien Wu Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan

Tetsuji Yokoyama Department of Human Resources Development, National Institute of Public Health, Saitama, Japan

Elena M. Yubero-Serrano Lipids and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatología Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain

Dmitry B. Zorov Lomonosov Moscow State University, A.N. Belozersky Institute of Physico-Chemical Biology, Moscow, Russia

Preface

In the past few decades there have been major advances in our understanding of the etiology of disease and its causative mechanisms. Increasingly it is becoming evident that free radicals are contributory agents: either to initiate or propagate the pathology or add to an overall imbalance. Furthermore, reduced dietary antioxidants can also lead to specific diseases and pre-clinical organ dysfunction. On the other hand, there is abundant evidence that dietary and other naturally occurring antioxidants can be used to prevent, ameliorate or impede such diseases. The science of oxidative stress and free radical biology is rapidly advancing and new approaches include the examination of polymorphism and molecular biology. The more traditional sciences associated with organ functionality continue to be explored but their practical or translational applications are now more sophisticated.

However, most textbooks on dietary antioxidants do not have material on the fundamental biology of free radicals, especially their molecular and cellular effects on pathology. They may also fail to include material on the nutrients and foods which contain antioxidative activity. In contrast, most books on free radicals and organs disease have little or no text on the usage of natural antioxidants.

The series **Oxidative Stress and Dietary Antioxidants** aims to address the aforementioned deficiencies in the knowledge base by combining in a single volume the science of oxidative stress and the putative therapeutic usage of natural antioxidants in the diet, its food matrix or plants. This is done in relation to a single organ, disease or pathology. These include cancer, addictions, immunology, HIV, aging, cognition, endocrinology, pregnancy and fetal growth, obesity, exercise, liver, kidney, lungs, reproductive organs, gastrointestinal tract, oral health, muscle, bone, heart, kidney and the CNS.

In the present volume, **Aging: Oxidative Stress and Dietary Antioxidants**, holistic information is imparted within the structured format of two main sections:

1. **Oxidative Stress and Aging**
2. **Antioxidants and Aging**

The first section on **Oxidative Stress and Aging** covers the basic biology of oxidative stress, from molecular biology to physiological pathology. Topics include markers of frailty, skin aging, cardiovascular disease, the liver, arthritis and diabetes. The second section, **Antioxidants and Aging**, covers cellular and molecular processes of vegetarian diets, enteral nutrition, natural antioxidants in foods and the diet, herbs and spices, coenzyme Q10, vitamins C and D, S-equol, zinc, magnesium, tryptophan, melatonin-enriched foods and lycopene. There is also material on the aging processes, age-related pathologies and organ systems, including menopause, physical performance, skin, bone and osteoporosis, the brain and neurodegeneration, the cardiovascular system, diabetes, muscle, arthritis, inflammation, mitochondria and leukocytes. The aforementioned provide a detailed framework for understanding the relationships between aging, oxidative stress and dietary components. However, more scientifically vigorous trials and investigations are needed to determine the comprehensive properties of many of these antioxidants, food items or extracts, as well as any adverse properties they may have.

The series is designed for dietitians and nutritionists, and food scientists, as well as health care workers and research scientists. Contributions are from leading national and international experts including those from world-renowned institutions.

*Professor Victor R. Preedy,
King's College London*

Contents

Contributors ix

Preface xiii

1

OXIDATIVE STRESS AND AGING

1. Oxidative Stress and Frailty: A Closer Look at the Origin of a Human Aging Phenotype

I-CHIEN WU, CHAO A. HSIUNG, CHIH-CHENG HSU,
XI-ZHANG LIN

Introduction 3

Oxidative Stress and Aging 4

Frailty 4

Oxidative Stress and Frailty 6

Unanswered Questions 12

Conclusion and Future Perspectives 12

Summary Points 13

References 13

2. Skin Aging and Oxidative Stress

JOHN M. STARR, ROBERT J. STARR

Introduction 15

The Structure of Human Skin 15

Measuring Skin Aging 16

Cellular Correlates of Skin Aging 16

Oxidative Stress and Intrinsic Skin Aging 17

Environmental Exposures Associated
with Skin Aging 18

Photoaging 19

Conclusions 21

Summary Points 21

References 21

3. Cardiovascular Disease in Aging and the Role of Oxidative Stress

FAWAZ ALZAID, VINOOD B. PATEL, VICTOR R. PREEDY

Introduction 23

Physiology of the Aging Cardiovascular
System 25

The Molecular Basis of Oxidative Stress as Applied to the
Cardiovascular System 26

Longevity Genes and the Longevity Network 29

Other Genes and Pathways in Oxidative Stress and Age-Related
Cardiovascular Diseases 33

Summary Points 36

References 36

4. Oxidative Stress, Aging and Mitochondrial Dysfunction in Liver Pathology

SYLVETTE AYALA-PEÑA, CARLOS A. TORRES-RAMOS

Introduction 39

Evidence for Age-Associated Morphologic, Structural and
Functional Changes in the Liver 40

Evidence for Age-Associated Loss of Mitochondrial Bioenergetics
in Liver 40

Oxidative Stress and Antioxidant Responses in Liver Aging 41

Oxidative Damage to the Nuclear and Mitochondrial Genomes in
Liver Aging 43

Mitochondrial Dysfunction and Liver-Associated Disease 45

Conclusion 47

Summary Points 47

References 47

5. Arthritis as a Disease of Aging and Changes in Antioxidant Status

RAHUL SAXENA

Introduction 49

The Concept of Oxygen Toxicity and Free Radicals 50

Oxidative Stress in Arthritis 52

Summary Points 57

References 58

6. Diabetes as a Disease of Aging, and the Role of Oxidative Stress

DIPAYAN SARKAR, KALIDAS SHETTY

Introduction 61

Type 2 Diabetes and Aging 61

The Role of Oxidative Stress in Human Disease 65

Oxidative Stress in Type 2 Diabetes and Aging 65

Conclusion 68

Summary Points 68

References 68

2

ANTIOXIDANTS AND AGING

7. Oxidative Stress and Antioxidants in Elderly Women

BRUNNA CRISTINA BREMER BOAVENTURA,
PATRICIA FARIA DI PIETRO

Introduction 73

Role of Estrogen in Oxidative Stress and Antioxidant Defense in
Elderly Women 73

Role of Telomere Length in Oxidative Stress and Antioxidant Defense in Elderly Women	74
Dietary Antioxidant Therapies in Elderly Women	75
Summary Points	78
References	78

8. Antioxidants, Vegetarian Diets and Aging

S. WACHTEL-GALOR, P.M. SIU, L.F.F. BENZIE

Introduction	81
Human Aging: Why and How Does It Occur, and What Are the Consequences of Aging?	81
Oxidative Stress and Aging	82
Lowering Oxidative Stress: The Potential Role of Dietary Antioxidants in Increasing Healthspan	84
Antioxidants in Food	85
Vegetarian Diet, Antioxidants, Oxidative Stress and Healthspan	87
Antioxidants and Health: Molecular Connections and Research Needs	88
Summary Points	90
References	90

9. Enteral Nutrition to Increase Antioxidant Defenses in Elderly Patients

JOSÉ EDUARDO DE AGUILAR-NASCIMENTO

Introduction	93
Enteral Nutrition in Elderly Patients	93
Enteral Nutrition with Antioxidant Properties	94
Enteral Nutrition with Whey Protein	94
The Role of Vitamins and Micronutrients with Antioxidant Properties	95
Conclusion	97
Summary Points	97
References	97

10. Herbs and Spices in Aging

SUHAILA MOHAMED

Introduction	99
Spices	99
Herbs	102
Seaweeds	104
Summary Points	105
References	106

11. Coenzyme Q₁₀ as an Antioxidant in the Elderly

ELENA M. YUBERO-SERRANO, ANTONIO GARCIA-RIOS,
JAVIER DELGADO-LISTA, PABLO PÉREZ-MARTINEZ,
ANTONIO CAMARGO, FRANCISCO PEREZ-JIMENEZ,
JOSE LOPEZ-MIRANDA

Oxidative Stress and Antioxidant Defense	109
Aging	109
Coenzyme Q ₁₀	110
Conclusions	115
Summary Points	115
References	115

12. Vitamin C and Physical Performance in the Elderly

KYOKO SAITO, ERIKA HOSOI, AKIHITO ISHIGAMI,
TETSUJI YOKOYAMA

Introduction	119
Oxidative Stress and Exercise	120
Oxidative Stress, Vitamin C Supplementation, and Physical Performance	121
Epidemiology Study	121
Intervention Study	124
Conclusions	126
Summary Points	126
References	126

13. Tryptophan and Melatonin-Enriched Foodstuffs to Improve Antioxidant Status in Aging

M. GARRIDO, A.B. RODRÍGUEZ, M.P. TERRÓN

Introduction	129
Dietary Tryptophan and Melatonin: Sources of Health	130
Consumption of Foodstuffs Containing Bioactive Compounds to Protect Against Oxidative Stress	133
Summary Points	134
Acknowledgments	134
References	134

14. Protective Effects of Vitamin C on Age-Related Bone and Skin Phenotypes Caused by Intracellular Reactive Oxygen Species

SHUICHI SHIBUYA, HIDETOSHI NOJIRI, DAICHI MORIKAWA, HIROFUMI KOYAMA, TAKAHIKO SHIMIZU

Introduction	137
<i>Sod1</i> Deficiency Induces Bone Loss	138
Vitamin C Prevents Bone Loss in <i>Sod1</i> -Deficient Mice	138
Vitamin C Improves Bone Loss Induced by Estrogen Deficiency	140
Mechanical Unloading Induces ROS Production and Bone Loss	140
Skin Atrophy in <i>Sod1</i> -Deficient Mice	140
A Vitamin C Derivative Improves Skin Atrophy in <i>Sod1</i> -Deficient Mice	141
Summary Points	142
References	142

15. S-Equol, an Antioxidant Metabolite of Soy Daidzein, and Oxidative Stress in Aging: A Focus on Skin and on the Cardiovascular System

RICHARD L. JACKSON, JEFFREY S. GREIWE, RICHARD J. SCHWEN

Introduction	145
Properties of S-Equol	146
Aging Skin	148
Isoflavones and Aging Skin	148
S-Equol's Mechanism of Reducing Oxidative Stress in Skin	149
S-Equol and Cardiovascular Diseases	149
S-Equol's Mechanism for Reducing Oxidative Stress in the Cardiovascular System	151

Importance of S-Equol Exposure Early in Life	152
Summary Points	153
References	153

16. Magnesium, Oxidative Stress, and Aging Muscle

MARIO BARBAGALLO, LIGIA J. DOMINGUEZ

Introduction	157
Magnesium Metabolism in Older Adults	158
Magnesium, Muscular Performance, and Aging Muscle	159
Magnesium, Exercise, and Oxidative Stress	161
Magnesium, Oxidative Stress, and the Aging Muscle: The Role of Inflammation	161
Magnesium, Immune Responses, and Oxidative Stress	162
Consequences of Magnesium Imbalance with Age	162
Conclusions	163
Summary Points	163
References	164

17. Late-Life Depression and Antioxidant Supplements

JOANNA RYBKA, KORNELIA KEDZIORA-KORNATOWSKA,
FLOOR VAN HEESCH, JOZEF KEDZIORA

Introduction	167
Antioxidants and Neuropsychologic Functions in the Elderly: Evidence for Antidepressant Activity	168
Summary Points	174
References	174

18. Antioxidant and Anti-Inflammatory Role of Melatonin in Alzheimer's Neurodegeneration

SERGIO A. ROSALES-CORRAL, RUSSEL J. REITER, DUN-XIAN TAN,
LUCIEN C. MANCHESTER, XIAOYAN LIU

Introduction	177
Melatonin: Synthesis and Mechanisms of Action	178
How Free Radicals Are Formed	181
Some Oxidative-Stress-Related Facts About the Brain	183
Where Do Free Radicals Come from in the Alzheimer's Disease Brain?	183
How Does Melatonin Scavenge Free Radicals?	187
Melatonin Stimulates Antioxidant Systems	189
Breaking the Cycle Neuroinflammation \leftrightarrow Oxidative Stress	190
Melatonin: An Anti-A β Agent	190
Melatonin Production Decreases with Age	191
Conclusions	191
References	191

19. Mitochondria-Targeted Antioxidants and Alzheimer's Disease

VLADIMIR P. SKULACHEV, NIKOLAY K. ISAEV, NADEZHDA A. KAPAY,
OLGA V. POPOVA, ELENA V. STELMASHOOK, KONSTANTIN G. LYAMZAEV,
IRINA N. SHARONOVA, DMITRY B. ZOROV, VLADIMIR G. SKREBITSKY

Introduction	195
Mitochondrial Reactive Oxygen Species as Probable Mediators of the Abeta-Induced Damage to Alzheimer's Disease Neurons	196
Mitochondria-Targeted Antioxidants Reduce the Toxic Effects of Abeta in Models of Alzheimer's Disease	196

Mitochondria-Targeted Antioxidants Improve Neurologic Recovery After Traumatic Brain Injury or Stroke and Reduce the Risk of Developing Alzheimer's Disease	198
The Geroprotective Effect of SkQ1	199
Summary Points	199
Acknowledgment	199
References	199

20. Downregulation of the Prooxidant Heart Failure Phenotype by Dietary and Nondietary Antioxidants

VICTOR FARAH, RAZA ASKARI, SHADWAN ALSAFWAH,
DWIGHT A. DISHMOM, SYAMAL K. BHATTACHARYA, KARL T. WEBER

Introduction	203
Congestive Heart Failure: A Prooxidant Phenotype	204
Antioxidants Downregulate the Prooxidant Heart Failure Phenotype	206
Summary and Conclusions	208
Summary Points	209
Acknowledgment	209
References	209

21. Overview of the Role of Antioxidant Vitamins as Protection Against Cardiovascular Disease: Implications for Aging

KOUTATSU MARUYAMA, HIROYASU ISO

Introduction	213
Effects of Aging on Cardiovascular Disease	213
Primary Preventive Effects of Antioxidant Vitamins for CVD	214
Secondary Preventive Effects and Therapeutic Effects of Antioxidant Vitamins for CVD	220
Effect of Modification Factors	222
Conclusion	222
Summary Points	222
References	222

22. Hypertension, Menopause and Natural Antioxidants in Foods and the Diet

MARIA GRAZIA MODENA

Introduction	225
Oxidative Stress and Hypertension: Hidden Mechanisms	225
Menopause, Oxidative Stress and Hypertension: Pink Networking	226
Natural Antioxidant Agents	226
Conclusions	229
Summary Points	229
References	229

23. Aging and Arthritis: Oxidative Stress and Antioxidant Effects of Herbs and Spices

M.S. MEKHA, R.I. SHOBHA, C.U. RAJESHWARI, B. ANDALLU

Introduction	233
Types of Free Radical and Their Generation	233
The Phenomenon of Oxidative Stress	234
Oxidative Stress in Diseases	234
Aging and Diseases	234

Antioxidant Systems	237
Traditional Medicine and Herbs	237
Summary Points	244
References	244

24. Lycopene and Other Antioxidants in the Prevention and Treatment of Osteoporosis in Postmenopausal Women

L.G. RAO, N.N. KANG, A.V. RAO

Introduction	247
Osteoporosis	247
Oxidative Stress	247
Antioxidants	248
Studies on the Antioxidants Polyphenols and Lycopene	250
General Summary and Conclusion	255
Acknowledgments	257
References	257

25. Zinc, Oxidative Stress in the Elderly and Implications for Inflammation

ANANDA S. PRASAD

Introduction	259
Discovery of Zinc Deficiency in Humans	259
Clinical Manifestations of Zinc Deficiency	261
Zinc Deficiency in Elderly Subjects	261
Proposed Concept of Mechanism of Zinc Action as an Antioxidant and Anti-Inflammatory Agent	270
Summary Points	272
References	274

26. Antioxidant Supplementation in the Elderly and Leukocytes

DAVID SIMAR, CORINNE CAILLAUD

Introduction	277
Changes in the Immune System During Aging	277
The Role of Oxidative Stress in Immune Senescence	279
Effects of Antioxidants on the Immune System During Aging	282
Conclusion	285
Summary Points	285
References	286

27. Metabolic Mobilization Strategies to Enhance the Use of Plant-Based Dietary Antioxidants for the Management of Type 2 Diabetes

DIPAYAN SARKAR, KALIDAS SHETTY

Introduction	289
The Role of Dietary Antioxidants and Plant Phenolics in the Management of Type 2 Diabetes	289
Inhibitory Activities of Different Plant-Based Foods on α -Amylase and α -Glucosidase	292
Enhancement and Mobilization of Plant-Based Antioxidants, Including Phenolics	293
Conclusion	295
Summary Points	295
References	295

Index 297



SECTION 1

OXIDATIVE STRESS AND AGING

Oxidative Stress and Frailty: A Closer Look at the Origin of a Human Aging Phenotype

I-Chien Wu, Chao A. Hsiung, Chih-Cheng Hsu

Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan

Xi-Zhang Lin

Department of Internal Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

List of Abbreviations

ATM ataxia-telangiectasia mutated
ATR ataxia telangiectasia and Rad3-related
BER base excision repair
BubR1 mitotic checkpoint serine/threonine-protein kinase BUB1 beta
CDC25 cell-division cycle 25
CHK1 checkpoint kinase 1
CHK2 checkpoint kinase 2
CREBH cyclic AMP response element binding protein hepatocyte
CuZnSOD copper/zinc superoxide dismutase (SOD1)
DDR DNA-damage response
DHEA dehydroepiandrosterone
DHEAS dehydroepiandrosterone sulfate
eNOS endothelial nitric oxide synthase
ER endoplasmic reticulum
IκB inhibitor of kappa B
IKK1 inhibitor of nuclear factor kappa-B kinase subunit alpha
IKK2 inhibitor of nuclear factor kappa-B kinase subunit beta
IL-2 interleukin-2
IL-6 interleukin-6
IL-8 interleukin-8
IRS-1 insulin receptor substrate-1
JNK kinases c-jun N-terminal kinases
MDA malondialdehyde
MnSOD Mn-superoxide dismutase (SOD2)
MPT mitochondrial permeability transition
mtDNA mitochondrialDNA
MTH1 mutT human homolog 1
NADPH reduced form of nicotinamide adenine dinucleotide phosphate
NER nucleotide excision repair
NF-κB nuclear factor-κB
nNOS neuronal nitric oxide synthase
NUDT5 Nudix (nucleoside diphosphate linked moiety X)-type motif 5
8-OHdG 8-hydroxy-2'-deoxyguanosine
ROS reactive oxygen species
TNF-α tumor necrosis factor-α
WRN Werner protein

INTRODUCTION

Oxidative stress, defined as a disturbance in the prooxidant-antioxidant balance leading to oxidative damage,¹ has a key role in aging. More importantly, an increasing amount of evidence suggests that oxidative stress acts causally in the pathogenesis of numerous age-dependent and age-related chronic diseases. Over the past few decades, frailty has been increasingly recognized as a major health problem for older adults. As a distinct pathologic state, frailty contributes to numerous poor health outcomes independently of diseases and disability, and it is characterized by clinical presentations which are well defined and easily identifiable. Because of years of research, we have a better understanding of the system-level pathogenesis of frailty. It is becoming clear that frailty may have its origin in the fundamental aging process. Oxidative stress could play a crucial role in the cellular-level pathogenesis of frailty. In this chapter, the relationship between oxidative stress and frailty is delineated. To address this issue comprehensively, we attempt to integrate the results from human studies and model organism experiments. After a brief overview of oxidative stress in aging, the better known system-level abnormalities associated with the frailty syndrome are introduced. We then discuss whether and how oxidative stress at cellular levels causes frailty. Finally, we present a model of frailty pathogenesis incorporating the current understanding of frailty at the levels of molecules, cells, organs, and systems.

OXIDATIVE STRESS AND AGING

Aging represents 'progressive deterioration during the adult period of life that underlies an increasing vulnerability to challenges and a decreasing ability of an organism to survive'.² The deterioration is due to progressive accumulation of unrepaired damage and has the following core features: intrinsicity, universality, progressiveness and irreversibility, and it is genetically programmed.² The literature suggests that oxidative stress is the major cause of somatic damage.² Denham Harman proposed the free-radical theory of aging in 1956, which states that aging results from random deleterious damage to tissue by free radicals. His theory is among the most acknowledged theories of aging.³ Since then, an increasing amount of evidence has indicated that oxidative stress increases with age and contributes to numerous age-related pathologic processes.⁴

The laboratory model organism experiments provide direct evidence that supports the importance of oxidative stress in aging. Numerous mutations that extend the lifespan of yeast, worms, flies, and mice have elevated antioxidant defenses and reduced oxidative stress. In yeast, major mutations that extend replicative and/or chronologic lifespans involve Ras-AC-PKA or Tor-Sch9 signaling.⁵ Lifespan extension associated with altered activities in these pathways has been shown to require the antioxidant enzyme superoxide dismutase (Mn-SOD), which scavenges superoxide free radicals.⁵ In *Caenorhabditis elegans*, lifespan extension can be achieved by reducing the activities of insulin/IGF-like signaling pathways (e.g. *age-1* and *daf-2* mutants), thereby activating the Forkhead FoxO transcription factor *daf-16*.⁶ Active DAF-16 promotes the transcription of major antioxidant genes, including genes encoding catalases, MnSOD, and CuZnSOD. These antioxidants are necessary for lifespan extension in these mutant worms.⁶ As in yeast and worms, insulin/IGF1 signaling pathways affect longevity in mice. Acting downstream of IGF receptors, p66^{Shc} enhances production of mitochondrial reactive oxygen species (ROS) by catalyzing redox reactions, which yield hydrogen peroxide.⁷ Deleting p66^{Shc} in mice results in decreased oxidative stress, which correlates with an increased lifespan.⁷

Results of human studies are congruent with the findings of model organism experiments. An age-related increase in oxidative damage to macromolecules has been observed in humans.⁸ DNA variants in the genes that modulate oxidative stress were linked to longevity.^{9,10}

FRAILTY

Definition

As an extreme phenotype of human aging, frailty is a state of increased vulnerability with a decreased ability to maintain homeostasis.¹¹ Although it can be compounded by disease or disability, this vulnerability is primarily age related and is caused by a reduced reserve capacity of interconnected physiologic systems that adapt to stressors, leading to a breakdown of homeostasis.¹¹ Despite the lack of a clear consensus, there are several operational definitions of frailty in the literature; these definitions are based on different theories on the underlying causes of frailty. Comprehensive reviews of the definition of frailty are beyond the scope of this article and can be found elsewhere.¹¹ Two commonly used definitions are discussed.

According to the operational definition of *frailty phenotype* proposed by Fried et al, a person is considered frail if three or more of the following five criteria are present: unintentional weight loss, muscle weakness, slow walking speed, low physical activity, and exhaustion (Table 1.1).¹² Older adults with one or two of the criteria are considered prefrail, whereas those without any criteria are considered robust.¹² Being the commonly cited operational definition in frailty research, the frailty phenotype is based on the assumption that frailty arises

TABLE 1.1 Frailty Phenotype According to Fried et al^{12 a}

Criteria	Frailty Characteristic	Measure
1	Weight loss (unintentional)	>10 lbs lost unintentionally in prior year (reported)
	Shrinking	
	Sarcopenia	
2	Muscle weakness	Grip strength below cutoff value, ¹² adjusted for gender and body mass index
3	Exhaustion	Answering 'moderate or most of the time' to 'I feel that everything I do is an effort' or 'I cannot get going'.
	Poor endurance	
4	Slow walking speed	Walking speed below cutoff value, ¹² based on time to walk 15 feet, adjusting for gender and standing height.
5	Low physical activity	Kilocalories expended per week below cutoff value (383 kcal/wk in men; 270 kcal/wk in women) ¹²

^aAn individual is considered frail if three or more of the five criteria are present. People with one or two of the criteria are considered prefrail, whereas those without any criteria are considered robust.

from unique pathologic processes that are independent of diseases and disability. Previous research has shown that the frailty phenotype is able to predict adverse health outcomes independently of disease and disability, and frail older adults are at greater risk compared with prefrail adults.¹² Moreover, there are clues that specific pathophysiologic processes lead to the development of frailty in the absence of disease.¹³

Unlike the Fried definition, Rockwood et al hypothesized that frailty arises from the accumulation of potentially unrelated diseases, subclinical dysfunctions, and disability, and represents an intermediary mechanism linking these conditions to poor health outcomes.¹⁴ The concept of frailty being a distinct pathologic state, separate from diseases and disability, is less emphasized. Frailty is defined by a frailty index, which is created by counting the number of health deficits in an older adult. The health deficits can be any clinical symptom, sign, disease, disability, laboratory, imaging, or other examination abnormality.¹⁴ Using this definition, frailty is associated with poor health outcomes in different populations.¹⁵

Clinical Significance

The prevalence of frailty is high. It is estimated that a minimum of 10–25% of people aged 65 years and older (and 30–45% of those aged 85 years and older) are frail.¹² Frailty is the core issue in healthy aging and geriatric

medicine. In contrast to the younger population, the older population is characterized by a greater variation in health status, outcomes, or response to therapy, which cannot be explained by age and disease alone.¹⁶ As a measure of biologic age, frailty permits superior risk prediction in older adults compared with chronologic age and diseases. Regardless of the operational definitions used, it has been repeatedly demonstrated that, compared with age and chronic diseases, frailty stratification is more strongly associated with an older adult's risk of poor outcomes, including infections, disabilities, institutionalization, and death.^{12,15}

Organ and System Abnormalities Associated with Frailty

As described, frailty is caused by abnormal interconnected physiologic systems, which are essential for maintaining homeostasis. The key physiologic systems currently known to be involved in frailty pathogenesis include the musculoskeletal system (skeletal muscle), metabolism (adiposity, insulin activity), immune system (inflammation), endocrine system (insulin-like growth factor-1, dehydroepiandrosterone sulfate, and testosterone), and autonomic nervous system (Fig. 1.1).¹¹

Sarcopenia

Body composition changes with age. An age-related loss of skeletal muscle mass is termed sarcopenia.¹⁷

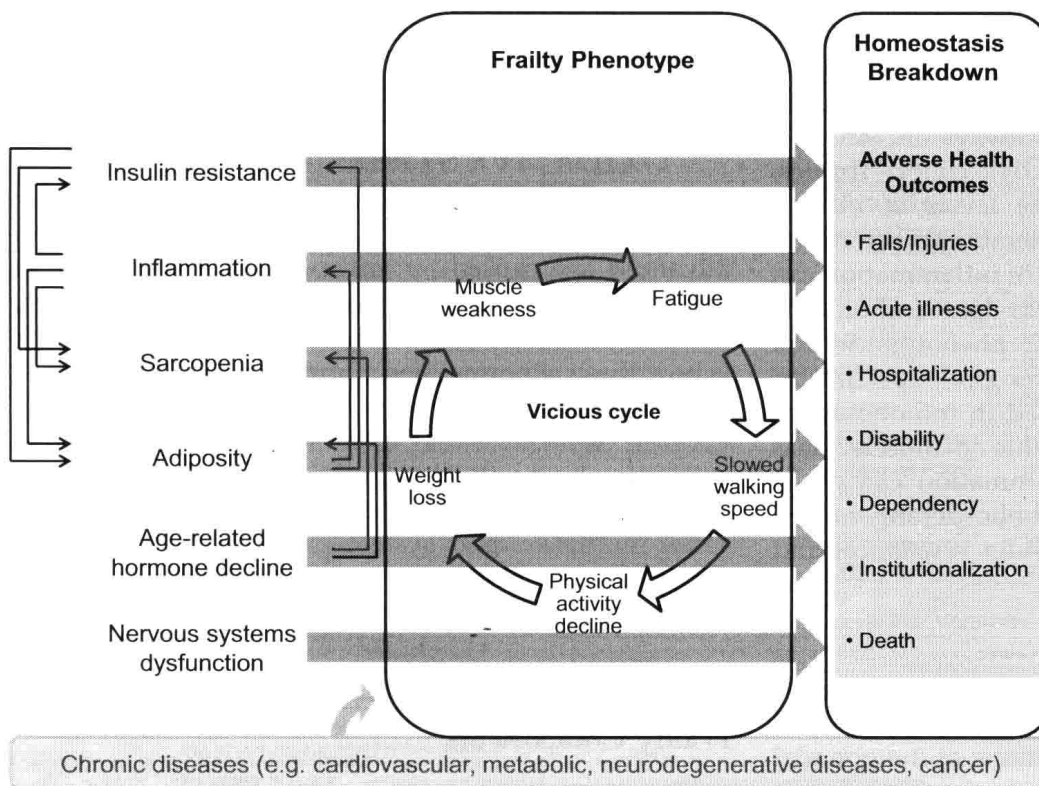


FIGURE 1.1 Organ and system abnormalities associated with frailty. As a human aging phenotype, frailty is characterized by an increased likelihood of homeostasis breakdown. Frailty, either alone or in the presence of diseases, predicts future adverse health outcomes in older adults. Previous research has suggested that several organ/system abnormalities are responsible for homeostasis breakdown at an advanced age, and frailty may represent the clinical manifestations of the pathogenic processes. The key pathogenic processes are (i) insulin resistance; (ii) inflammation; (iii) sarcopenia; (iv) adiposity; (v) age-related hormone decline; and (vi) nervous system dysfunction.¹¹ These processes are interrelated, and a vicious cycle typically develops. Subclinical diseases may have a role in frailty development.¹⁶