

Nutrition and Health

Series Editor: Adrienne Bendich

Ronald Ross Watson

Sherma Zibadi *Editors*

Bioactive Dietary Factors and Plant Extracts in Dermatology

 Humana Press

NUTRITION AND HEALTH SERIES

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Editors

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Preface

Historically, as well as recently, research is showing that foods, dietary supplements, and some nutrients are important in skin cancer prevention and skin health. Within the 48 chapters of this book two major needs are fulfilled by defining the role of dietary supplements, foods, and nutrients in treatment and prevention of skin cancer and dermal damage. A major focus is on the primary causes of dermal damage: aging and solar exposure in seven focused areas of skin health promotion.

Initially broad overviews of diet and food in skin health are reviewed. Thus the role of foods found in the Mediterranean diet and probiotics are documented to affect the skin and prevent damage. In addition overview chapters are included on the effects of ultraviolet irradiation (UV) which cause significant damage and cancer in were included the skin.

The book's second section describes the role of selected nutrients in promoting skin health and preventing dermal diseases. Diet and nutrition are vital keys to controlling morbidity and mortality from chronic diseases. Thus taurine and omega 3 fatty acids can aid in ameliorating psoriasis and this is documented in reviews. In addition, antioxidant actions of vitamin C and nitric oxide produced from supplemental arginine are keys to dermal health.

Then key researchers in the third section describe the role of herbs and plant spices in skin health. Turmeric and ginger are documented to function in skin care. In addition an Indian indigenous berry and Aloe vera's roles in dermatology are described.

The fourth section has detailed reviews of selected dietary components in dermal health. Polyphenols as a group with components from grapes, chocolate, and other nutrient rich botanicals are explored as examples. Antioxidants also play roles in skin functions. Specifically, resveratrol, rice bran, and coenzyme Q10 are discussed. Antioxidants in dietary supplements and nutraceutical foods counteract some of the damaging effects of UV (ultraviolet) radiation (light) in skin and other tissues. They play key roles in preventing the development of skin cancer. UV light is clearly the major cause of skin cancers as well as aging, damaged skin. Therefore experts reviewed the roles of bioactive foods and their constituents to reduce UV-induced skin cancer and dermal damage.

The fourth section focuses on historic vitamins with well-defined effects on skin and skin cancer where new research is providing new insights. Thus folate, vitamin D, and vitamin E on skin cancer are reviewed. These are readily available agents that have multiple effects on health and frequently used as supplements.

The fifth and major section investigates research and focuses on the two major types of skin cancer: melanoma and basal cell carcinoma. Skin cancer is the most common form of cancer and dietary materials can play a key role. The U.S. National Institutes of Health report that only 18 % of adults meet the recommended intake of vegetables. Increasingly, Americans, Japanese, and Europeans are turning to the use of dietary vegetables, medicinal herbs, and their extracts or components to prevent or treat cancer. It has been known for decades that those populations with high plant consumption

have reduced risks of cancers. Therefore important foods in skin health and cancer prevention are reviewed. These include Indian foods, chocolate, green tea and its components, licorice, fruit antioxidants, mangosteen, soybeans, and polyacetylenes in carrots. In addition the multitude of complex biomolecules as dietary extracts in dietary fruits and vegetables play a crucial role in skin health maintenance. Experts review dietary supplements in general as well as specific ones including *N*-acetylcysteine, turmeric, and polyphenols in general.

The final section is extensive in its review of plants and their components in preventing and treating skin diseases. There is a huge cosmetic and skin care industry for damage that does not result in cancer. Here antioxidant dietary materials may be particularly useful in prevention or as ingredients in medications to combat solar and aging effects. Specific issues confronting older Americans include challenges of how to deal with changes in skin texture, health, and, especially, cancer. The U.S. Bureau of Census predicts that seniors are increasing dramatically and will more than double to 80 million by 2050, at which time there will be nearly 2 billion seniors worldwide. It is critical that these additional years are productive, enjoyable, and disease free. Antioxidants and their food and herbal sources should play critical roles in this process. Antioxidants in dietary vegetables and their products often have limited harmful side effects. This stands in stark contrast to many drugs that are promoted and studied for possible disease-preventive activity. A wide variety of herbs including ginger, vitamins, Indian native plant remedies, foods, including chocolate, and well-recognized herbs, including aloe vera, are reviewed by experts. Mechanisms of actions including molecular sensors and mediators in skin cancer, and insulinotropic signaling in psoriasis and atopic dermatitis are defined.

Plant extracts as dietary supplements are now a multibillion-dollar business, built upon limited research data. Common dietary vegetables and herbs and their over-the-counter extracts are readily available. Therefore this book is useful to the growing nutrition, food science, and natural product research and development community. This book focuses on the growing body of knowledge on the role of various dietary plant constituents that reduce oxidative damage as part of chronic disease. Expert reviews define and support the actions of bioflavonoids, antioxidant vitamins, and similar materials that are part of dietary vegetables, dietary supplements, herbs, and nutraceuticals.

Finally, the volume editors would like to extend their appreciation to Springer and their staff for providing the professional platform of communication for new, challenging ideas and hypotheses in nutritional sciences. Similarly appreciation is extended to the series editor Adrienne Bendich for her personal input in positioning the book toward the right audience and also her incisive and pertinent comments, recommendations, and suggestions for improving the presentation, content, and cohesion.

Tucson, AZ, USA

Ronald Ross Watson, Ph.D.
Sherma Zibadi, Ph.D.

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patients' as well as health professionals' questions, which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, has the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Bioactive Dietary Factors and Plant Extracts in Dermatology," edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, is a very welcome addition to the Nutrition and Health Series. The 48 chapters in this comprehensive volume include chapters that examine the role of essential and nonessential dietary components on skin health, skin care, skin cancers, and other dermatological diseases. The book is logically organized into seven sections and begins with an overview section that includes five informative chapters. The first chapter, on the Mediterranean diet and skin health, informs us that people from Mediterranean regions have one of the lowest melanoma rates in Europe. Several of the bioactive plants and plant components of the Mediterranean diet, including herbs, vitamin C, vitamin E, *n*-3 polyunsaturated fats from extra virgin oil and blue fish, and anthocyanins and flavonoids from red oranges, are reviewed in depth in subsequent chapters. The second chapter provides important safety data concerning the potential for certain dietary factors and plant extracts to trigger some immune-mediated skin disorders including autoimmune and hypersensitivity reactions. Sun exposure provides UV radiation that can adversely affect the skin if exposure is prolonged and skin is not protected. Several dietary components have been shown to protect skin from UV damage and these are reviewed in the next chapter. Skin changes have been documented as consequences of metabolic diseases including diabetes and obesity, as reviewed in the fourth chapter. Diabetes-associated skin changes include inflammation, immune dysfunction, imbalanced epidermal homeostasis, and other skin disorders. Obesity is associated with changes in skin barrier function, sebaceous gland and sebum production, wound healing as well as acanthosis nigricans, and skin tags that may be associated with

insulin resistance. The final chapter in the overview section is unique in its examination of the role of probiotics in skin health. Several clinical trials have shown an association between probiotic supplementation and the management of atopic dermatitis. Thus, the chapter reviews the immunological mechanisms affected by probiotics, beyond the gut, that may benefit the skin.

The second section contains four chapters that describe the roles of certain vitamins, fatty acids, and amino acids in maintaining the health of the skin as well as their effects in certain skin diseases. The chapter on the importance of vitamin C to skin health reminds us that vitamin C is essential to the formation of collagen and that its antioxidant properties enhance the potential for reduction in UV skin damage. Omega-3 fatty acids, given as a supplement or as an intravenous infusion, have been shown to reduce psoriatic lesions of the skin. This new area of clinical research is summarized in the next chapter. Arginine, a nonessential amino acid (and sometimes considered as a conditionally essential amino acid), is metabolized to nitric oxide. This nitric oxide metabolic pathway has been found in several cell types that reside in the skin including keratinocytes, melanocytes, Langerhan's cells, fibroblasts, and endothelial cells. Taurine is also considered as a conditionally essential amino acid, and recent clinical studies with taurine-containing compounds have shown some benefits when given orally or used topically in several skin conditions.

The third section on dietary components and skin care contains four chapters that examine the potential for certain foods and food components to affect skin functions. The plant components are used internally, externally, or in some cases, can be used both ways. The substances reviewed in individual chapters include turmeric, ginger, amla, and aloe vera. These plants and the plant parts have been used to treat various skin ailments for centuries in Chinese, Ayurvedic, Tibetan, Unani, Srilankan, Arabic, and African traditional medicines. The authors of these chapters review the mechanisms of action of the plants and plant extracts, as well as the major bioactive components and examine pre-clinical studies and, where available, clinical data related to the assessment of skin quality as well as wound healing, UV blocking, treatment and/or prevention of psoriasis, skin aging and skin cancer. Although all of these plants have been used to treat conditions affecting many aspects of health, with respect to the skin, observational as well as preclinical and some clinical studies have shown these four plants to have skin care properties such as preventing signs of skin ageing, acne, psoriasis, enhancing wound healing, reducing UV-induced skin damage, and reducing the effects of chemically induced carcinogenesis in animal models.

There are many dietary components that affect skin health. The next section highlights eight dietary components and their effects on the functioning of the skin. This Series has a whole volume devoted to "*Chocolate in Health and Nutrition*," edited by Ronald Ross Watson, Victor R. Preedy, and Sherma Zibadi. The first chapter in the section examines the role of chocolate in skin health. Other substances reviewed include oats and its constituents (*Avena sativa*) in a chapter that includes excellent tables, figures and 86 up-to-date references, resveratrol, grape seed extracts, coenzyme Q10, and rice bran. Skin health is discussed with respect to increased elasticity, tonicity and/or firmness, reduced wrinkle width and/or volume, reduced fine lines, increased hydration, decreased skin roughness, decreased scaling, improved skin structure and barrier function, and depigmentation of age-related skin spots. Conditions discussed include extra dry, itchy skin (xerosis), and dry skin associated with diabetes, as well as associated pruritus (itching), eczema, UV-induced skin damage and acne. Data included in these chapters are derived from preclinical as well as clinical studies where available. Administration of the substances can be via oral intake and/or topical applications. Several chapters examine novel oral and topical delivery systems to enhance the bioavailability of the substances.

Skin cancer is generally divided into two categories: melanoma and non-melanoma skin cancers. Non-melanoma skin cancers include basal cell carcinoma and squamous cell carcinoma. Basal cell carcinoma is the most common form of skin cancer and rarely spreads to other tissues. Squamous cell carcinoma cells have the ability to invade other tissues of the body. Melanoma is not as common as the two types of carcinomas but it is the most lethal form of skin cancer. This volume contains 14

chapters that review the role of dietary factors in skin cancer development and treatment. Several chapters specifically examine melanoma as this is considered the most serious type of skin cancer.

The fifth section, containing three chapters, reviews the data on essential nutrients (folate, vitamin D, and vitamin E) and their potential to affect skin cancer as preventive as well as therapeutic agents. The chapter on folate, with nine excellent figures and 135 relevant references, indicates that folate nutrient levels support many biochemical processes important for the maintenance and function of healthy skin. When dietary folate intakes are low and/or skin folate levels are depleted, there are associated findings of increased risk of psoriasis, vitiligo, dermatitis, and skin cancers. The precursor of the active form of vitamin D is synthesized in the sun-exposed skin. Although low vitamin D status is associated with increased risk of many cancers, increased sun exposure is associated with increased risk of skin cancers. This well-referenced and illustrated chapter carefully balances the recommendations for safe levels of UV exposure with the dietary recommendations for assuring optimal vitamin D status.

Eleven chapters are devoted to examining the role of dietary factors and their components and dietary supplements in skin cancer development and/or treatment. The first three chapters in this section provide broad overviews of the potential mechanisms of action of plant molecules and describe the models used to test the activities of these bioactive components. Specific chapters review findings using components of grapes, milk thistle, citrus peel, tomatoes, bitter melon, marigold, peach, soy, carrots, chocolate, turmeric, and green tea. Certain components that are found in a number of these foods include flavonoids that have been shown to have chemopreventive properties. Specifically discussed are apigenin, genistein, silymarin, quercetin, and *N*-acetylcysteine. Certain non-flavonoid polyphenols also have been shown to have chemopreventive activities such as resveratrol, curcumin, and epigallocatechin-3-gallate (EGCG). These chapters examine the current body of research and include detailed information about cellular targets, research from *in vitro* and laboratory animal studies and clinical data when available. Safety data from clinical studies are included in addition to potential efficacy findings.

The final section of the volume mainly examines the importance of plants and plant extracts in the care of non-cancerous skin diseases. The majority of the unique chapters describe plants that have been used in India as part of the Ayurvedic medicine tradition. Each plant is described using its botanical name and the uses of each plant part are described. This section contains 13 chapters that review skin diseases including psoriasis, atopic dermatitis, acne, parasitic skin diseases, fungal, viral, and bacterial skin diseases as well as systemic diseases that result in skin changes. Substances not examined in earlier chapters include licorice, Indian gooseberry, East Indian globe thistle, mangosteen, neem, karanja oil, heartleaf moonseed and Indian ginseng. A number of the chapters review findings from non-Western cultures where tropical fruits, herbs and spices have been used as components of salves and lotions as well as oral solutions for thousands of years but without the benefit of well-controlled trials that would provide valuable information with regard to dosing, duration of use as well as safety data.

In addition to the chapters on plants, the in-depth chapter by Melnik, which includes over 200 references, examines the overall effect of Western diets and obesity on the development of the major classes of skin diseases. This chapter, as well as the chapter by Sabetisoofyani that links leptin levels with increased risk of melanoma, remind us that total dietary caloric intake above recommended intake levels increases the risk of many serious diseases including some that affect the skin. The final chapter in this comprehensive volume examines the potential for orally administered probiotics to be of benefit in the treatment of atopic dermatitis. The chapter includes an extensive review of the immunology of the skin and the complexity of treating atopic dermatitis as this disease may involve fungal as well as bacterial infections and is thought to have a genetic component as well as neuropathology. The chapter includes over 130 relevant references and detailed tables that summarize both the laboratory animal models as well as clinical studies using specific probiotics in the treatment of chronic dermatological diseases.

The logical sequence of the sections as well as the chapters within each section enhance the understanding of the latest information on the role of dietary components and therapeutically used plants in the care of the skin under healthy as well as skin disease condition. The volume contains unique chapters that are helpful for clinicians, related health professionals including the dietician, nurse, pharmacist, physical therapist, behaviorist, psychologist, and others involved in the treatment of many different racial and ethnic population groups with skin conditions as well as serious skin diseases. This comprehensive volume has great value for academicians involved in the education of graduate students and postdoctoral fellows, medical students, and allied health professionals who plan to interact with patients and/or clients with relevant dermatological disorders.

The volume contains over 100 detailed tables and figures that assist the reader in comprehending the complexities of skin physiology as well as the details of many of the plants used to treat skin conditions. The overriding goal of this volume is to provide the health professional with balanced documentation and awareness of the newest research and therapeutic approaches including an appreciation of the complexity of the skin's responses to UV-induced trauma, infections, and diseases. Hallmarks of the 48 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. There are over 2,000 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics, treatments and preventive strategies that are involved in the understanding of how skin conditions may affect healthy individuals as well as those with chronic diseases. Of equal importance, critical issues that involve patient concerns, such as UV exposure, potential effects of immunological, psychological, and neurological functions, are included in well-referenced, informative chapters. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of various preventive and treatment options that are available today as well as in the foreseeable future.

In conclusion, "*Bioactive Dietary Factors and Plant Extracts in Dermatology*," edited by Ronald Ross Watson, Ph.D. and Dr. Sherma Zibadi, M.D., provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and comprehensive volume on the current state of the science and clinical practice involving plants used as foods as well as therapeutics in the maintenance of healthy skin and the treatment of skin diseases. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrienne Bendich, Ph.D., F.A.C.N., F.A.S.N.

Series Editor Bios



Dr. Adrienne Bendich has recently retired as Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare where she was responsible for leading the innovation and medical programs in support of many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK’s support for the Women’s Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. Dr. Bendich is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich, who is now President of Consultants in Consumer Healthcare LLC, is the editor of ten books including “*Preventive Nutrition: The Comprehensive Guide For Health Professionals*,” fourth edition, coedited with Dr. Richard Deckelbaum, and is the Series Editor of *Nutrition and Health* for Springer/Humana Press (www.springer.com/series/7659). The Series contains 40 published volumes—major new editions in 2010–2011 include *Vitamin D*, second edition edited by Dr. Michael Holick; *Dietary Components and Immune Function* edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; *Bioactive Compounds and Cancer* edited by Dr. John A. Milner and

Dr. Donato F. Romagnolo; *Modern Dietary Fat Intakes in Disease Promotion* edited by Dr. Fabien DeMeester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; *Iron Deficiency and Overload* edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; *Nutrition Guide for Physicians* edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; *Nutrition and Metabolism* edited by Dr. Christos Mantzoros, and *Fluid and Electrolytes in Pediatrics* edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include *Handbook of Drug-Nutrient Interactions* edited by Dr. Joseph Boullata and Dr. Vincent Armenti; *Probiotics in Pediatric Medicine* edited by Dr. Sonia Michail and Dr. Philip Sherman; *Handbook of Nutrition and Pregnancy* edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; *Nutrition and Rheumatic Disease* edited by Dr. Laura Coleman; *Nutrition and Kidney Disease* edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; *Nutrition and Health in Developing Countries* edited by Dr. Richard Semba and Dr. Martin Bloem; *Calcium in Human Health* edited by Dr. Robert Heaney and Dr. Connie Weaver, and *Nutrition and Bone Health* edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich served as Associate Editor for *Nutrition*, the International Journal; served on the Editorial Board of the *Journal of Women's Health and Gender-Based Medicine*, and was a member of the Board of Directors of the American College of Nutrition.

Dr. Bendich was the recipient of the Roche Research Award, is a *Tribute to Women and Industry* Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences, 2000–2001. In 2008, Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. Dr. Bendich holds academic appointments as Adjunct Professor in the Department of Preventive Medicine and Community Health at UMDNJ and has an adjunct appointment at the Institute of Nutrition, Columbia University P&S, and is an Adjunct Research Professor, Rutgers University, Newark Campus. She is listed in Who's Who in American Women.

Volume Editors Bios



Ronald Ross Watson, Ph.D., attended the University of Idaho but graduated from Brigham Young University in Provo, Utah, with a degree in chemistry in 1966. He earned his Ph.D. in biochemistry from Michigan State University in 1971. His postdoctoral schooling in nutrition and microbiology was completed at the Harvard School of Public Health, where he gained 2 years of postdoctoral research experience in immunology and nutrition.

From 1973 to 1974, Dr. Watson was assistant professor of immunology and performed research at the University of Mississippi Medical Center in Jackson. He was assistant professor of microbiology and immunology at the Indiana University Medical School from 1974 to 1978 and associate professor at Purdue University in the Department of Food and Nutrition from 1978 to 1982. In 1982 Dr. Watson joined the faculty at the University of Arizona Health Sciences Center in the Department of Family and Community Medicine of the School of Medicine. He is currently professor of health promotion sciences in the Mel and Enid Zuckerman Arizona College of Public Health.

Dr. Watson is a member of several national and international nutrition, immunology, cancer, and alcoholism research societies. Among his patents he has one on a dietary supplement; passion fruit peel extract with more pending. He had done DHEA research on its effects on mouse AIDS and immune function for 20 years. He edited a previous book on melatonin (Watson RR. *Health Promotion*

and Aging: The Role of Dehydroepiandrosterone (DHEA). Harwood Academic Publishers, 1999, 164 pages). For 30 years he was funded by Wallace Research Foundation to study dietary supplements in health promotion. Dr. Watson has edited more than 100 books on nutrition, dietary supplements and over-the-counter agents, and drugs of abuse as scientific reference books. He has published more than 500 research and review articles.



Dr. Sherma Zibadi received her Ph.D. in nutrition from the University of Arizona and is a graduate of the Mashhad University of Medical Sciences, where she earned her M.D. She has recently completed her post-doctoral research fellowship awarded by the American Heart Association. Dr. Zibadi engages in the research field of cardiology and complementary medicine. Her main research interests include maladaptive cardiac remodeling and heart failure, studying the underlying mechanisms and potential mediators of remodeling process, which helps to identify new targets for treatment of heart failure. Dr. Zibadi's research interest also extends into alternative medicine, exploring the preventive and therapeutic effects of natural dietary supplements on heart failure and its major risk factors in both basic animal and clinical studies, translating lab research finding into clinical practice. Dr. Zibadi is an author of multiple research papers published in peer-reviewed journals and books, as well as coeditor of several books.

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The work of Dr. Watson's editorial assistant, Bethany L. Stevens, and Humana's project manager, Maureen Alexander, in communicating with authors, working with the manuscripts and the publisher was critical to the successful completion of the book and is much appreciated. Their regular responses to queries and collection of manuscripts and documents were extremely helpful. Support for Ms. Stevens' work was graciously provided by the National Health Research Institute (nonprofit). It is part of its mission to communicate to scientists about bioactive foods and dietary supplements was vital (<http://www.naturalhealthresearch.org>). Such support and was part of the Institute's efforts to educate scientists and the lay public on the health and economic benefits of nutrients in the diet as well as supplements. Finally Mari Stoddard of the Arizona Health Sciences library was instrumental in helping find the authors and their addresses in the early stages of the book's preparation. The support of Humana Press staff as well as the input by the series editor, Adrienne Bendich, is greatly appreciated for the improved organization of this book.

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Part I

Overview

Chapter 1

Mediterranean Diet and Skin Health

Laura Primavesi, Marta Piantanida, and Valerio Pravettoni

Key Points

- Mediterranean diet includes similar cooking traditions from regions bordering the Mediterranean sea. This diet encourages high intake of fruits, vegetables, and legumes and low consumption of red meat and saturated fats.
- As people from Mediterranean regions present one of the lowest melanoma rates, Mediterranean diet can be extremely helpful to providing skin protection.
- This dietary approach may be recommended particularly during early childhood, for populations with high risk to develop skin diseases, and for individuals with high UVR exposure and/or compromised immunity.
- The most interesting bioactive components of the Mediterranean diet include carnosol from herbs like sage and rosemary, vitamin C together with vitamin E, *n*-3 polyunsaturated fats from extra virgin oil and blue fish, and anthocyanins and flavonoids from red oranges.

Keywords Mediterranean diet • Dietary antioxidant supplementation • Carnosol • Red orange complex • Vitamin C • Vitamin E • Carotenoids • Hydroxytyrosol • *n*-3 Polyunsaturated fats • UV radiation

Mediterranean Diet: Definition

The Mediterranean diet (MD) represents a complex series of centuries-old nutritional habits typical of the regions bordering the Mediterranean Sea. One of the first scientists to study the MD was Ancel Keys (1904–2004), who hypothesized that different kinds of dietary fats could have different effects on health. He observed a lower mortality rate due to cardiovascular diseases in Southern Europe and Northern Africa than in Northern Europe and the United States [1].

The most commonly known version of the MD is graphically represented by a food pyramid, first presented in the mid-1990s and based on food patterns typical of Crete and Southern Italy. Briefly, this diet emphasizes high consumption of vegetables, fruit, legumes, and unrefined cereals, moderate

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consumption of dairy products (mostly as cheese and yogurt), moderate to high consumption of fish, low consumption of meat and meat products (in particular reducing consumption of red meat), and moderate wine consumption. Fats represent approximately 25–35% of the MD total calories, almost exclusively constituted by olive oil instead of butter, margarine, and other saturated fats comprising only 8% or less of the daily caloric intake [2].

We aim to highlight that the MD constitutes not only a mere food chart but represents a set of skills, knowledge, practices, and traditions promoting social interaction and a healthy lifestyle. Latest versions of the MD include at the base of the food pyramid the following concepts: physical activity, conviviality, and seasonal and local consuming. On account of this fact in 2010, the United Nations Educational, Scientific and Cultural Organization (UNESCO) included the MD in the representative list of the intangible cultural heritage of humanity.

In the following paragraphs, we focus our attention on peculiar MD food components considered to have a photoprotective effect. We prefer to start with major natural sources because nutraceutical properties of bioactive molecules are often enhanced by a synergic effect that occurs in the food matrix.

Mediterranean Herbs

In the MD, an important role is played by Mediterranean herbs, including rosemary (*Rosmarinus officinalis* L.), sage (*Salvia officinalis* L.), basil (*Ocimum basilicum* L.), and oregano (*Origanum vulgare* L.). Their flavorful leaves are commonly used to season meals and reduce salt content. These herbs are very rich in diterpenes, recently discovered to be phytochemicals because of their functional properties, such as their antimicrobial, antioxidant, anti-inflammatory, and anticancer activities. One of the most investigated and promising molecules is carnosol, an ortho-diphenolic diterpene with an abietane carbon skeleton with hydroxyl groups in the C11 and C12 position and a lactone moiety across the B ring. This compound is derived from the oxidative degradation of carnosic acid. Carnosol and carnosic acid together represent approximately up to 5% of the dry weight of rosemary leaves and account for more than 90% of their antioxidant properties [3].

Huang and colleagues [4] evaluated the effect of a methanol extract from dried rosemary leaves on tumor onset and promotion in mice skin. To induce tumor onset, the mice were topically treated on their backs with benzo(a)pyrene (BP) and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) once or twice a week. In a group of animals topically treated with 1.2 mg or 3.6 mg of rosemary extract 5 min prior to each application, the number of tumors per mouse decreased by 54–64%. In contrast, topical application of BP+TPA in mice not treated with rosemary extract resulted in 7.1 tumors per mouse. The application of rosemary extract on mouse skin also inhibited TPA-induced ornithine decarboxylase activity, TPA-induced inflammation, arachidonic acid-induced inflammation, TPA-induced hyperplasia, and TPA-induced tumor promotion. Other mice were treated with 7,12-dimethylbenz(a)anthracene (DMBA) and TPA. In addition, in mice pretreated with rosemary extract (0.4, 1.2, and 3.6 mg), the number of TPA-induced skin tumors was reduced per mouse by 40%, 68%, and 99%, respectively. In contrast, mice without rosemary extract application developed an average of 17.2 skin tumors per mouse. The authors also investigated the effect of a topical application of carnosol or ursolic acid isolated from rosemary. Carnosol (1, 3, and 10 μmol) and ursolic acid (0.3, 1, or 2 μmol) inhibited the number of skin tumors per mouse in DMBA-pretreated mice by 38%, 63%, and 78%, and by 45–61%, respectively. Thus, rosemary extract seems to have a stronger inhibitory effect on tumor promotion than carnosol or ursolic acid alone, suggesting that combinations of these compounds together with other rosemary constituents are responsible for inhibitory effects against tumors. In conclusion, topical application of rosemary extract inhibited the covalent binding of BP to skin and the tumor onset by BP and DMBA.

Offord and colleagues [5] investigated the protective effect of carnolic acid against UVA-induced photodamage in a cell culture system. Human dermal fibroblasts, derived from a young male with skin type III (brown hair, brown eyes), were treated with several nanoparticle formulations containing dietary antioxidant alone or in mixture to preserve their properties. This treatment was performed 24 h before UVA irradiation of a typically minimal erythemal dose in human skin to allow penetration into cells. UVA irradiation led to a 10- to 15-fold increase in metalloproteinase 1 expression, considered a marker of potential collagen degradation and photoaging. This increase was suppressed in the presence of low micromolar concentrations of vitamin E, vitamin C, or carnolic acid. Heme-oxygenase 1 expression, a general marker of cellular oxidative stress, was also strongly induced by UVA irradiation but none of the antioxidants inhibited this effect at the concentrations used in this study.

Recently, Russo and coinvestigators [6] demonstrated the ability of a rosemary extract, containing 31.7% of carnolic acid, 0.4% rosmarinic acid, and 5.9% of carnosol, to counteract the adverse effects of UV radiation. Consistent with prior studies, at concentrations of 10–80 $\mu\text{g}/\text{mL}$, this extract was able to significantly reduce the growth of two melanoma cell lines in a dose-dependent manner. In addition, this study provided the first evidence that rosemary extract reduces the growth of human cancer cells by triggering an apoptotic process. In fact, melanoma cells exposed to methanol rosemary extract demonstrated high DNA fragmentation but no necrosis, which was indicated by no statistically significant increase in cytoplasmic lactate dehydrogenase (LDH) release.

Citrus Fruit

In the MD, citrus fruit is much more important than any other fruits and vegetables. Seven countries in the Mediterranean basin, including Spain, Italy, and Egypt, are in the top 20 producers of the sweet orange (*Citrus sinensis* L.), the most commonly grown fruit tree in the world. A total of 68.5 million tons of this orange was produced worldwide in 2008 (<http://faostat.fao.org>). Red or blood oranges are named for their juice, which is reminiscent of blood, and cultivated since the fifteenth century in Sicily (Italy); they represent a natural variety of sweet oranges with an abnormal pigmentation that gives the pulp a streaked red color. Important varieties of blood oranges are *Tarocco*, *Sanguinello*, and *Moro*, which grow almost exclusively in Sicily's Etna area. From these fruits, a "red orange complex" (ROC) has been chromatographically purified and investigated [7] because of its peculiar composition, which is characterized by high levels of anthocyanins, flavanones, ascorbic acid, and hydroxycinnamic acids. A possible explanation of the peculiar photoprotective role of these compounds is that they naturally play an important resistance to the UVA and UVB sun irradiation by the plant photosynthetic apparatus.

Cardile and colleagues [7] analyzed the *in vitro* anti-inflammatory activity of ROC at concentrations of 10 and 100 $\mu\text{g}/\text{mL}$ on normal human keratinocytes exposed to interferon-gamma (IFN- γ) and histamine, used to enhance the effects of IFN- γ . Keratinocytes initiate and regulate inflammatory and immune skin responses, releasing different cytokines and expressing membrane molecules that are able to modulate permanence and activation of T lymphocytes into epidermis. Normal keratinocytes stimulated by IFN- γ and histamine expressed membrane molecules, such as intercellular adhesion molecule-1 (ICAM-1), and released inflammatory soluble factors, such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8). Unstimulated cell lines did not produce these inflammatory molecules.

Moreover, the authors compared ROC activity to hydrocortisone. Incubation of cell lines with IFN- γ and histamine for 48 h induced strong expression of ICAM-1, and the addition of ROC at different concentrations together with IFN- γ and histamine induced dose-dependent inhibition of ICAM-1 expression. At the highest concentration (100 $\mu\text{g}/\text{mL}$), ROC blocked $40 \pm 4\%$ of ICAM-1 expression. Hydrocortisone led to a reduction of $28 \pm 6\%$ of ICAM-1 expression, not significantly