Advances in Biochemistry in Health and Disease

Paramjit S. Tappia
Anureet K. Shah
Naranjan S. Dhalla *Editors*

# Lipophilic Vitamins in Health and Disease

Springer

# Advances in Biochemistry in Health and Disease

Volume 28

Advances in Biochemistry in Health and Disease focus on the latest developments in biochemical research with implications for health and disease. This book series consists of original edited volumes and monographs, presented by leading experts in the field and provides an up to date and unique source of information for all those interested in the fundamental, biochemical processes of the latest and emerging topics and techniques.

Covering a wide variety of topics, this book series is a valuable source of information from those at the lab bench through to the Health Care workers.

Paramjit S. Tappia · Anureet K. Shah ·
Naranjan S. Dhalla
Editors

# Lipophilic Vitamins in Health and Disease

Springer

*Editors*
Paramjit S. Tappia
Asper Clinical Research Institute
St. Boniface Hospital
Winnipeg, MB, Canada

Naranjan S. Dhalla
Institute of Cardiovascular Science
St. Boniface Hospital Albrecthsen
Research Centre
Winnipeg, MB, Canada

University of Manitoba
Winnipeg, MB, Canada

Anureet K. Shah
Department of Nutrition and Food Science
California State University Los Angeles
Los Angeles, CA, USA

ISSN 2512-2142 ISSN 2512-2150 (electronic)
Advances in Biochemistry in Health and Disease
ISBN 978-3-031-55488-9 ISBN 978-3-031-55489-6 (eBook)
https://doi.org/10.1007/978-3-031-55489-6



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Paper in this product is recyclable.

# Preface

There are 13 vitamins essential for human health and are grouped according to whether they are soluble in non-polar solvents (lipophilic) or in water (hydrophilic). The focus of this book will be on the lipophilic vitamins. Much is known about the cellular and metabolic actions of lipophilic vitamins, which are designated by the letters A, D, E and K. Vitamin K is, for example, required for normal blood clotting. Vitamin A (retinol) is the precursor of retinal, the light-absorbing group in visual pigments. A deficiency of this vitamin results in night blindness. The metabolism of calcium and phosphorus is regulated by a hormone that is derived from vitamin D. Deficiency in vitamin D impairs bone formation during growth. Vitamin E protects unsaturated membrane lipids from oxidation. Since the lipophilic vitamins are involved in a wide variety of biological processes, these are considered as essential nutrients. In this book, the novel biochemical and molecular functions of lipophilic vitamins outside of traditional cellular roles will be highlighted in this book. It should be mentioned that while scientific and clinical exploration of lipophilic vitamins has escalated, it is clear that public awareness has also gained notable interest.

Accordingly, it is proposed to bring together international experts, from around the world, in the field of vitamins for human health and disease, to update and integrate current understanding on the effects of different lipophilic vitamins on cellular, metabolic and molecular biochemical reactions with respect to different pathophysiological conditions including cardiovascular disease, cancer, metabolic defects, inflammatory and immune diseases. While adequate amounts of vitamins are required for normal cell function their deficiencies are detrimental to human health, toxicity of the lipophilic vitamins can occur as they are stored in the tissues. This book will underscore the multifaceted functionality of lipophilic vitamins and yield a compilation of information from basic fundamental knowledge to advanced aspects of our understanding.

There are 20 chapters in three different parts in this book, comprising of Part I: General Aspects of Lipophilic Vitamins; Part II: Vitamin E and Associated Metabolites in Health and Disease and Part III: Functional Aspects of Vitamins A, D and K. Each chapter in the book will further advance the understanding of the effects of lipophilic vitamins on the biochemistry of the cellular function in health and disease. It is envisioned that this book will stimulate and motivate biomedical researchers and scientists to further explore the relationship between lipophilic vitamins and biological processes, as well as serve as a highly useful resource for nutritional investigators, health professionals, medical students, fellows, residents and graduate students.

This book will be uniquely positioned as it will focus on the biochemistry and molecular biology of lipophilic vitamins in diverse cell systems in relation to human health and disease. The intent of this volume is to provide current and basic understanding of the specific biochemical processes that are regulated by lipophilic vitamins that can regulate cell function. We hope that the reader will gain knowledge and further understanding of the importance of lipophilic vitamins. The novel insights provided by the contributing authors will assist in advancing preventive medicine worldwide as well as bring forward knowledge that may help in the use of lipophilic vitamins as adjuvant to therapeutic strategies for human disease.

We are grateful to the members of the Advisory Board for this series on "Advances in Biochemistry in Health and Disease" for the important and valuable suggestions. We would also like to thank the wonderful support of all the contributors as well as the enthusiastic efforts of Dr. Gonzalo Cordova for his time and commitment in evaluating and approving this project. In addition, we express our gratitude to Mr. Rajan Muthu and his team for the meticulous assistance and professionalism in the production of this book. We appreciate the infrastructural support provided by the St. Boniface Hospital Albrechtsen Research Centre for this project.

Winnipeg, Canada — Paramjit S. Tappia
Los Angeles, USA — Anureet K. Shah
Winnipeg, Canada — Naranjan S. Dhalla

# Contents

**Part I General Aspects of Lipophilic Vitamins**

**1 The Cardio-protective Effect of Fat-Soluble Vitamins on Anti-cancer Drug Induced Cardiotoxicity** . . . . . 3
Jamie S. Duarte and Anureet K. Shah

**2 Fat Soluble Vitamins in the Ocular, Cardiac, and Infectious Diseases: Myths and Misconceptions** . . . . . 19
Zahra Sepehri, Aliyeh Sargazi, Maysam Yousefi, Farkhonde Sarhaddi, Mehdi Sepehri, Anahita Behzadi, Sina Etemadi, Marjan Hedayatipour, Yeganeh Azhdari Moghaddam, Nima Javadi Aghdam, Kourosh Shahraki, Zohre Kiani, Nasrin Etesami Fard, Zohre Mohammadi, and Roxana Kaveh

**3 The Effects of Lipophilic Vitamins on Women's Heart Health** . . . . . 73
Huong Nguyen, Breno Lintz, and Inna Rabinovich-Nikitin

**4 Mitigation of Dementia and Alzheimer's Disease with Lipophilic Vitamins and Their Derivatives: Preclinical and Clinical Evidence** . . . . . 85
Dhruv Sanjay Gupta, Janvi Parekh, Daksh Sanjay Gupta, Harpal S. Buttar, Meena Chintamaneni, and Ginpreet Kaur

**5 Lipid-Soluble Vitamins: Their Roles in Cardiovascular Health and Diseases** . . . . . 107
Zachary L. Venn, Emmanuel Adu-Agyekum, and Keshore R. Bidasee

**6 Interactions Between Gut Microbiota and Lipophilic Vitamins in Health and Disease** . . . . . 127
Sayantap Datta, Krishna M. Boini, and Saisudha Koka

**Part II Vitamin E and Associated Metabolites in Health and Disease**

**7 The Potential Role of Tocotrienols Against Cardiovascular Diseases** ..... 149
Hoda Yeganehjoo, Neda Zamani, Sidharth Chitkara, and Anureet K. Shah

**8 Recent Progress on the Skeletal Research of Tocotrienol** ..... 163
Kok-Yong Chin

**9 Importance of Vitamin E and Its Metabolism for Health and Disease** ..... 181
Lisa Börmel, Anja R. Geisler, Stefan Lorkowski, and Maria Wallert

**10 Beneficial Effects of Vitamin E Combined with Antioxidants in Cardiovascular System Disorders: Experimental Evidence** ..... 201
Belma Turan

**11 Vitamin E for the Prevention and Treatment of Cardiovascular Disease** ..... 221
Shirley C. Fitzpatrick-Wong, Paramjit S. Tappia, and Naranjan S. Dhalla

**12 Vitamin E (Tocopherol): Implications in Cardiovascular Health and Neuroprotection** ..... 233
Ranganathan Parameswari, Mariadoss Arokia Vijaya Anand, Chau-Zen Wang, Ranganathan Babaujanarthanam, and Prithiviraj Nagarajan

**Part III Functional Aspects of Vitamins A, D and K**

**13 Retinoids and the Vitamin a Receptor STRA6 in Health and Disease** ..... 261
Vinesh Dhokia and Salvador Macip

**14 A Vitamin Treatment for Motor Neurone Disease** ..... 275
Arabella Baptie and Peter McCaffery

**15 Vitamin D and Its Role on Inflammation, Oxidative Stress and Cardiovascular Disease** ..... 291
Sandra M. Barbalho, Lance A. Sloan, Adriano C. Araujo, Lucas F. Laurindo, and Katia P. Sloan

**16 Vitamin D and Immune Function: Unraveling the Connections** ..... 313
Leena Rajathy Port Louis, Suganya Kannan, Deepa Shanmugham, Jeyakumar Balakrishnan, and Prithiviraj Nagarajan

**17 Maternal Vitamin D Levels During Gestation and Impact on Offspring's Risk of Non-communicable Diseases in Adulthood** ..... 341
Rohini Ravindran Nair and Surya Ramachandran

**18 Unveiling the Link of Vitamin D and Diverse Cardiovascular Disorders: Current Status and Future Prospective** ..... 355
Kuldeep Kumar, Swesha Chhabra, Vishal Kumar Vishwakarma, Sangeeta Yadav, Jagriti Bhatia, Nirmal Singh, and Harlokesh Narayan Yadav

**19 Environmental Pollution-Induced Vitamin D Deficiency and Its Impact on the Outcomes of Pregnancy** ..... 371
Garvita Parikh and Bhoomika Patel

**20 Extra-Hepatic Functions of Vitamin K** ..... 387
Kotaro Azuma and Satoshi Inoue

# Contributors

**Emmanuel Adu-Agyekum** Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE, USA

**Nima Javadi Aghdam** Department of Biology, York University, Toronto, Canada

**Adriano C. Araujo** Department of Biochemistry and Pharmacology, School of Medicine, University of Marília, São Paulo, Brazil;
Postgraduate Program in Structural and Functional Interactions in Rehabilitation—University of Marília, São Paulo, Brazil

**Mariadoss Arokia Vijaya Anand** Orthopedic Research Center, School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

**Kotaro Azuma** Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;
Department of Systems Aging Science and Medicine, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan

**Ranganathan Babaujanarthanam** Department of Biotechnology, Thiruvalluvar University, Serkadu, Vellore, Tamil Nadu, India

**Jeyakumar Balakrishnan** Central Research Laboratory, Vinayaka Mission's Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Karaikal, India

**Arabella Baptie** Institute of Medical Sciences, University of Aberdeen, School of Medicine, Medical Sciences and Nutrition, Foresterhill, Aberdeen, Scotland, UK

**Sandra M. Barbalho** Department of Biochemistry and Pharmacology, School of Medicine, University of Marília, São Paulo, Brazil;
Postgraduate Program in Structural and Functional Interactions in Rehabilitation—University of Marília, São Paulo, Brazil;
School of Food and Technology of Marilia, São Paulo, Brazil

**Anahita Behzadi** Health Services Management Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

**Jagriti Bhatia** Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

**Keshore R. Bidasee** Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA;
Environmental, Agricultural, Occupational Health and Toxicology, University of Nebraska Medical Center, Omaha, NE, USA;
Nebraska Redox Biology Center, Lincoln, Omaha, NE, USA

**Krishna M. Boini** Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX, USA

**Lisa Börmel** Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany;
Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD) Halle-Jena-Leipzig, Jena, Germany

**Harpal S. Buttar** Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

**Swesha Chhabra** Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

**Kok-Yong Chin** Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Malaysia

**Meena Chintamaneni** Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS, Mumbai, India

**Sidharth Chitkara** Department of Psychology, University of California, Los Angeles, CA, USA

**Sayantap Datta** Department of Pharmacological and Pharmaceutical Sciences, College of Pharmacy, University of Houston, Houston, TX, USA

**Naranjan S. Dhalla** Institute of Cardiovascular Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada;
Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada

**Vinesh Dhokia** Mechanisms of Cancer and Aging Laboratory, Department of Molecular and Cell Biology, University of Leicester, Leicester, UK

**Jamie S. Duarte** Department of Nutrition and Food Science, California State University Los Angeles, Los Angeles, CA, USA

**Sina Etemadi** Department of Health Management, Policy and Economics, Faculty of Management and Medical Information Sciences, Kerman University of Medical Sciences, Kerman, Iran

**Nasrin Etesami Fard** Department of Cardiology, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

**Shirley C. Fitzpatrick-Wong** Asper Clinical Research Institute, Winnipeg, MB, Canada;
St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada

**Anja R. Geisler** Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany;
Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD) Halle-Jena-Leipzig, Jena, Germany

**Daksh Sanjay Gupta** Vivekanand Education Society's College of Pharmacy, Chembur, Mumbai, Maharashtra, India

**Dhruv Sanjay Gupta** Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS, Mumbai, India

**Marjan Hedayatipour** Department of Health Management, Policy and Economics, Faculty of Management and Medical Information Sciences, Kerman University of Medical Sciences, Kerman, Iran

**Satoshi Inoue** Department of Systems Aging Science and Medicine, Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan;
Division of Systems Medicine and Gene Therapy, Saitama Medical University, Hidaka, Saitama, Japan

**Suganya Kannan** Central Research Laboratory, Vinayaka Mission's Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Karaikal, India

**Ginpreet Kaur** Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS, Mumbai, India

**Roxana Kaveh** School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

**Zohre Kiani** Department of Internal Medicine, Iran University of Medical Sciences, Tehran, Iran

**Saisudha Koka** Department of Pharmaceutical Sciences, Irma Lerma Rangel School of Pharmacy, Texas A&M University, Kingsville, TX, USA

**Kuldeep Kumar** Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

**Lucas F. Laurindo** Department of Biochemistry and Pharmacology, School of Medicine, University of Marília, São Paulo, Brazil;
Department of Biochemistry and Pharmacology, School of Medicine, Faculdade de Medicina de Marília (FAMEMA), São Paulo, Marília, Brazil

**Breno Lintz** Department of Physiology and Pathophysiology, Max Rady Faculty of Health Sciences, Rady College of Medicine, The Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada

**Stefan Lorkowski** Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany;
Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD) Halle-Jena-Leipzig, Jena, Germany

**Salvador Macip** Mechanisms of Cancer and Aging Laboratory, Department of Molecular and Cell Biology, University of Leicester, Leicester, UK;
FoodLab, Faculty of Health Sciences, Universitat Oberta de Catalunya, Barcelona, Spain

**Peter McCaffery** Institute of Medical Sciences, University of Aberdeen, School of Medicine, Medical Sciences and Nutrition, Foresterhill, Aberdeen, Scotland, UK

**Yeganeh Azhdari Moghaddam** Zahedan University of Medical Sciences, Zahedan, Iran

**Zohre Mohammadi** Department of Cardiology, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

**Prithiviraj Nagarajan** Department of Biotechnology, Thiruvalluvar University, Serkadu, Vellore, Tamil Nadu, India;
Department of Medical Biotechnology, Aarupadai Veedu Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Kirumampakkam, Puducherry, India

**Rohini Ravindran Nair** Department of Medical Biotechnology, Gujarat Biotechnology University, Gandhinagar, Gujarat, India

**Huong Nguyen** Department of Physiology and Pathophysiology, Max Rady Faculty of Health Sciences, Rady College of Medicine, The Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada

**Ranganathan Parameswari** Department of Biotechnology, Thiruvalluvar University, Serkadu, Vellore, Tamil Nadu, India

**Janvi Parekh** Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS, Mumbai, India

**Garvita Parikh** School of Medico-Legal Studies, National Forensic Sciences University, Gandhinagar, Gujarat, India;
School of Doctoral Studies and Research, National Forensic Sciences University, Gandhinagar, Gujarat, India

**Bhoomika Patel** School of Medico-Legal Studies, National Forensic Sciences University, Gandhinagar, Gujarat, India

**Leena Rajathy Port Louis** Department of Pharmacology, Aarupadai Veedu Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Kirumampakkam, Puducherry, India

**Inna Rabinovich-Nikitin** Department of Physiology and Pathophysiology, Max Rady Faculty of Health Sciences, Rady College of Medicine, The Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada

**Surya Ramachandran** Department of Medical Biotechnology, Gujarat Biotechnology University, Gandhinagar, Gujarat, India

**Aliyeh Sargazi** Zahedan Health Center, Zahedan University of Medical Sciences, Zahedan, Iran

**Farkhonde Sarhaddi** Department of Pathology, Zahedan University of Medical Sciences, Zahedan, Iran

**Mehdi Sepehri** Department of Computer, Sanabad Golbahar Institute of Higher Education, Golbahar, Khorasan Razavi, Iran

**Zahra Sepehri** Department of Internal Medicine, Zabol University of Medical Sciences, Zabol, Iran;
Department of Family Medicine, University of Manitoba, Winnipeg, Canada

**Anureet K. Shah** Department of Nutrition and Food Science, California State University Los Angeles, Los Angeles, CA, USA

**Kourosh Shahraki** Ophthalmic Plastic and Reconstructive Surgeries Fellowship, Ophthalmic Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

**Deepa Shanmugham** Department of Obstetrics and Gynecology, Aarupadai Veedu Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Kirumampakkam, Puducherry, India

**Nirmal Singh** Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Punjab, India

**Katia P. Sloan** Texas Institute for Kidney and Endocrine Disorders, Lufkin, TX, USA

**Lance A. Sloan** Texas Institute for Kidney and Endocrine Disorders, Lufkin, TX, USA;
University of Texas Medical Branch, Galveston, TX, USA

**Paramjit S. Tappia** Asper Clinical Research Institute, Winnipeg, MB, Canada;
St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada

**Belma Turan** Departments of Biophysics, Faculty of Medicine, Lokman Hekim University, Ankara, Turkey

**Zachary L. Venn** Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA

**Vishal Kumar Vishwakarma** Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

**Maria Wallert** Institute of Nutritional Sciences, Friedrich Schiller University Jena, Jena, Germany;
Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD) Halle-Jena-Leipzig, Jena, Germany

**Chau-Zen Wang** Orthopedic Research Center, School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan;
Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan;
Regeneration Medicine and Cell Therapy Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan;
Department of Physiology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan;
Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan;
College of Professional Studies, National Pingtung University of Science and Technology, Pingtung, Taiwan

**Harlokesh Narayan Yadav** Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

**Sangeeta Yadav** Department of Pharmacology, Baba Saheb Ambedkar Medical College, New Delhi, India

**Hoda Yeganehjoo** Department of Clinical Nutrition, School of Health Professions, University of Texas Southwestern Medical Center, Dallas, TX, USA

**Maysam Yousefi** Research Center of Tropical and Infection Diseases, Kerman University of Medical Science, Kerman, Iran;
Department of Internal Medicine, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran

**Neda Zamani** Women's College Research Institute, Women's College Hospital, University of Toronto, Toronto, ON, Canada;
Institute of Medical Science, University of Toronto, Toronto, ON, Canada

# Part I
# General Aspects of Lipophilic Vitamins

# Chapter 1
# The Cardio-protective Effect of Fat-Soluble Vitamins on Anti-cancer Drug Induced Cardiotoxicity

**Jamie S. Duarte and Anureet K. Shah**

**Abstract** Anti-tumor medications like chemotherapies fall into the class of drugs referred to as anthracyclines. These anthracyclines, while powerful and effective in dealing with tumor growth have a degenerative effect on the cardiovascular system. Many cancer patients suffer from cardiomyopathy years after treatment with these drugs have been halted. However, an overwhelming number of patients still succumb to heart disease after surviving their initial bouts with cancer. An overwhelming amount of peer-reviewed research has looked into the use of fat-soluble vitamins specifically D and E as possible protectors of the heart in patients being treated with anthracycline. Vitamin D and E have been shown to have a significant statistical effect on many biomarkers that are affected by anthracycline cardiotoxicity. Both fat-soluble vitamins show a potential significant clinical effect that merits a further investigation in order to understand the mechanisms and pathways responsible for anthracycline mediated cardiotoxicity and possible routes to cardio protection.

**Keywords** Vitamin D · Vitamin E · Cardiovascular diseases · Cardiotoxiciy · Chemotherapy · Anthracyclines · Cardio-protection

## Introduction

The evidence surrounding chemotherapy-induced cardiotoxicity has been well studied [1–3]. While certain chemotherapy drugs have been used as the frontline treatment for many hematologic cancers and solid tumors; the effectiveness of drugs have been limited by the cardiotoxicity that arises because of their usage [4]. Levels of cardiotoxicity are related to dose–response although small doses have also resulted in cardiotoxicity. It is also widely accepted that symptoms of cardiotoxicity can occur many years after cessation of the last treatment [5]. The type of cardiotoxicity falls in

J. S. Duarte · A. K. Shah (✉)
Department of Nutrition and Food Science, California State University Los Angeles, Los Angeles, CA, USA
e-mail: akaur23@calstatela.edu



P. S. Tappia et al. (eds.), *Lipophilic Vitamins in Health and Disease*, Advances in Biochemistry in Health and Disease 28, https://doi.org/10.1007/978-3-031-55489-6_1

the category of two groups depending on how the cell is affected. Type I cardiotoxicity is cellular death caused by necrosis or apoptosis. This is irreversible cell death. Type II is cardiotoxicity caused by reversible cellular dysfunction [6]. Vitamin D, a fat-soluble vitamin has been suggested to be a player in treating a number of cardiovascular conditions [7]. Epidemiologic and experimental observations have led some researchers investigating the cardioprotective effects of vitamin D on anticancer drug cardiotoxicity mainly anthracycline class drugs like doxorubicin [8]. This review article will explore previous studies that have examined mechanisms and signaling pathways of anthracycline induced cardiotoxicity and how fat-soluble vitamins might potentially be a solution to the cardiotoxicity caused by chemotherapies like doxorubicin and others.

## Chemotherapy Drugs Inducing Possible Mitochondrial Damage

While not completely understood, some of the instigators of doxorubicin induced cardiotoxicity is the production of reactive oxygen species followed by lipid peroxidation as a result of the free radicals. The myocardium is especially susceptible to oxidative damage due to low levels of antioxidant enzymes [9]. What has been understood is that anthracycline-induced cardiotoxicity happens through the increased amount of reactive oxygen species [10]. However, some researchers don't believe this to be the sole cause of cardiac tissue damage therefore, new research hopes to discover alternate pathways. Some examples of alternate pathways include disruption of energetic mechanisms. Specifically energetic mechanisms involving the mitochondria [11]. The integrity of mitochondrial function is of particular importance being that the ATP that is produced is used by cardiac cells by way of the electron transport chain [12]. Previous research has indicated that disruption to mitochondrial function has led to loss of energy production, loss of architectural integrity, and difficulties in maintaining metabolic demands [13]. Cardiolipin, a phospholipid with great importance in its role in energy metabolism in the mitochondrial membrane, has been indicated to have a role in anthracycline-mediated cardiomyopathy [14]. This is through doxorubicin's ability to bind to cardiolipin which in turn leads to the loss of integrity of the function, properties, and environment of many energetic mechanisms [15]. Doxorubicin-induced mitochondrial dysfunction is a major mechanism of doxorubicin that ultimately leads to cell damage or death. The mechanism that plays a role in this dynamin-related protein 1, DRP1. As previously mentioned, reactive oxygen species occupy many roles in how it causes degradation throughout the body [16]. The generation of ROS comes with its activation of DRP1 through phosphorylation at s616 subsequently leading to mitochondrial localization and fission induction. Conversely, the same phosphorylation of DRP1 at S637 inhibits mitochondrial fission [17].

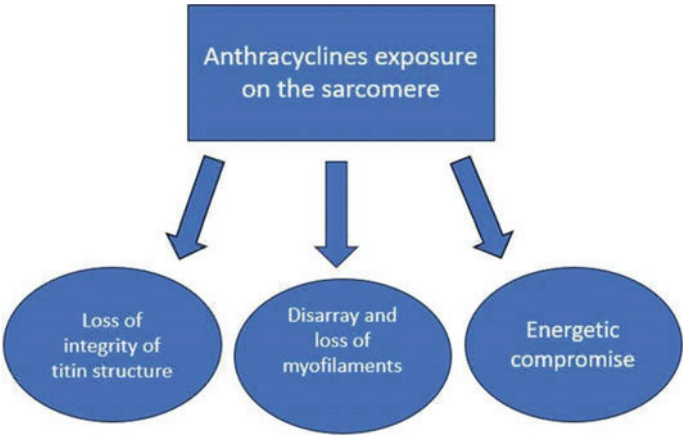


**Fig. 1.1** Consequences of anthracycline exposure on the sarcomere

## Disruption to the Sarcomere Structure

At the level of the sarcomere, cardiotoxicity here is characterized by disarray and loss of myofilaments. Anthracyclines are able to directly impact the structural, functional, and regulatory properties of the protein Titin [18]. Titin, the largest known protein in the human body, has a major role in maintaining the structure of the sarcomere [19]. As shown in, Fig. 1.1 anthracycline exposure is responsible for degenerating titin by way of proteolytic pathways affecting the energetic systems. Other in vitro studies have found that disarray and structural loss could be due to myocyte necrosis related to calpain-dependent pathways. In regard to titin degeneration as it relates to sarcomere disarray, the work of Chen et al. [20] observed the cardiac ankyrin repeat protein CARP or ANKRD1 was incredibly sensitive to doxorubicin directly leading to lowered CARP protein levels. The low levels were caused because of the inhibition of CARP transcription, a direct effect of the doxorubicin which would eventually lead to disruption of the sarcomere structure.

## Vitamin D3's Cytoprotective Effect Through Various Signaling Pathway

A 2021 study by Chen et al. [21] discovered that vitamin D3 attenuates cell cycle arrest and deterioration in human aortic endothelial cells (HAEC) caused by doxorubicin. Vitamin D3 protects HAEC against deterioration from the doxorubicin by increasing upregulation of IL-10. IL-10 has been well explored to reduce hypertension and inflammation-mediated senescence in the vascular system [22]. Senescence is the stopping of the cells ability to divide thus leading to dysfunction of vascular

tissue, vascular dysfunction, ramping of arteriosclerosis and in the end amplifies the damage potential for doxorubicin induced cardiotoxicity [23]. The exact signaling pathways involved were the SIRT1/FOXO3a signal pathways that acted by binding to the promoter region of IL-10 as indicated by the ChIP assay. The SIRT1/FOXO3a complexes act as a direct transcriptional promoter.

Another study involving vitamin D also aimed to investigate whether vitamin D can protect against cardiotoxic effects caused by chemotherapy in early breast cancer patients. 150 patients were divided into a control group and a group receiving vitamin D supplements in addition to chemotherapy. The study found that patients taking 0.5 μg of vitamin D had significantly lower levels for markers of heart damage and inflammation compared to the control group. Vitamin D has been shown to have a potential cardio-protective effect by suppressing pro-inflammatory cytokines and reducing the cytotoxic effects of chemotherapy [24]. Additionally, vitamin D has been shown to inhibit cell proliferation and angiogenesis in breast cancer cells. Research has shown that calcitriol can reduce the production of IL-6 by changing the p38 signaling pathway [25]. Furthermore, adding vitamin D to chemotherapy drugs can enhance their ability to kill cancer cells. Both in vitro and in vivo studies have demonstrated that adding vitamin D to doxorubicin treatment can reduce its cytotoxic effect, reduce heart damage, improve heart function, and reduce cardiac fibrosis by affecting reactive oxygen species production and modifying pro-inflammatory signaling pathways [26]. In the present study, IL-6 serum was significantly lowered in the vitamin D group compared to the control group. The downregulation of proinflammatory cytokines was also seen by increasing gene expression subsequently leading to a significant reduction of TNF-α and IL-6 in the blood. A similar experimental study by Awad et al. [27] found this same mechanism highlighting the obstruction of the inflammatory signal pathways and down regulation of IL-6.

One of the concerns when implementing a supplementation schedule is that the vitamins may affect the efficacy of cancer fighting anthracycline [28]. Despite the fact that it is a significant concern, some studies have been able to yield favorable results using adjuvant therapy involving fat soluble vitamins. Vitamin D protection mechanisms involve blocking C-MYC transcription through increased turnover of proteins or sequestration of b-catenin [29]. Unregulated, C-MYC caused by generation of ROS has been reported to induce expression of genes responsible for initiation and progression of disease [30]. In a 2021 study using mice treated with doxorubicin for triple negative breast cancer, fluorescence intensity showed a greater mean of C-MYC in a group of mice treated with 10 mg/kg compared to the group of mice that was given vitamin D + doxorubicin 10 mg/kg [8]. Immunoblot of cardiac tissue demonstrated an induced expression in mice treated with Dox (10 mg/kg) but lower NQO1 in mice treated with vitamin D in conjunction with their doxorubicin treatment enzyme NQO1 reduces quinones in order to protect cells from quinone-mediated ROS [31]. Lee et al. hypothesized a possible explanation for less NQO1 expression could have been the abundance of reactive oxygen species as a result of the vitamin D supplementation [32]. In the present study, analyzing immunoblots of cardiac tissue DRP1 phosphorylation at s616 was increased in the Dox (10 mg/kg) and decreased in the vitamin D + doxorubicin (10 mg/kg). Similarly, phosphorylation of DRP1 at s637

was increased with vitamin D but not with the dox group (mg/kg). Cleaved Caspase 3 was slightly increased with phosphorylation at s616 consistent with mitochondrial damage.

Doxorubicin treatment as it relates to the treatment of TNBC tumors in mice showed a lower tumor volume in the 6 mg/kg and 10 mg/kg treatment groups with doxorubicin. This treatment showed a dose-dependent effect was observed when comparing 6 mg/kg and 10 mg/kg groups. When including vitamin D in conjunction with both doxorubicin treatments the treatment was also statistically significant in reduction of tumor volume which would disprove the theory of vitamin D hindering the effectiveness of doxorubicin at least in this study. Use of Kaplan Meier curve indicated decreased survival in mice treated with dox 10 mg/kg with 50% surviving by day 16. When survival rates were compared among 10 mg/kg doxorubicin group and vitamin D + doxorubicin (10 mg/kg) the vitamin D intervention group showed improved survival rates and a similar survival rate between the vitamin D dox (6 mg/kg) and dox (6 mg/kg).

## Synergistic Effect of Pirfenidone and Vitamin D

Pirfenidone and vitamin D amelioration of cardiac fibrosis via Monocyte Chemoattractant Protein-1 and Jun N-terminal Kinase-1 pathways were explored on Ehrlich Ascites Carcinoma Bearing Mice. Both pirfenidone and vitamin D, either individually or in combination, were shown to decrease tumor weight and volume compared to the control group [26]. Pirfenidone is commonly used for the treatment of fibrosis and exerts anti-fibrotic and anti-inflammatory activities [33]. This study focused on new anti-fibrotic pathways involving JNK1 and MCP-1 pathways. In the present study the control group showed an increase in the levels of two inflammatory mediators, NF-κB and MCP-1 with ND-kB acting as the main transcription factor to regulate these molecules. Meanwhile, the group exposed to doxorubicin showed an increase in the levels of NF-κB and MCP-1, indicating that doxorubicin-induced inflammation is characterized by upregulation of these mediators. The effect of vitamin D on the JNK1 and MCP-1 signaling pathway may represent a novel mechanism for ameliorating fibrosis. Vitamin D has also been shown to have an anti-tumor effect by suppressing tumor angiogenesis, invasion, and metastasis [34]. In the study, the control group showed an increase in inflammatory mediators, including NF-κB and MCP-1, while doxorubicin-induced inflammation led to upregulation of NF-κB and MCP-1 expressions [26]. Vitamin D deficiency may lead to hypertrophy of cardiomyocytes followed by interstitial inflammation and fibrosis. In another study, the anti-inflammatory effect of vitamin D is attributed to breaking the nuclear factor kappa B (NF-κB) pathway, which regulates both acute and chronic inflammation and subsequent fibrogenesis [35]. Other studies show vitamin D's ability to target estrogen signaling pathways in breast cancer epithelial through downregulation of estrogen receptor alpha [36, 37].

### *Safety Efficacy of High-Dose Vitamin D Supplementation*

In elderly patients with aggressive B-cell lymphoma, vitamin D deficiency has been a reported negative prognostic factor [38]. One clinical trial reported that vitamin D supplementation might improve the outcome in cancer patients suffering from aggressive B-cell lymphoma. This trial reported a vitamin D3 supplementation schedule of 3570 IU/day which is under the 10,000 IU/day limit that has been proposed to have no adverse effects in healthy individuals [39]. Despite supplementation of vitamin D above the recommended dose of 2000 IU/day, half of the test results from this study showed that the patient's 25(OH)D levels were lower than normal. These results may suggest an unexplored pathway among patients undergoing immunochemotherapy and corticosteroid intervention that would require cancer patients to have increased vitamin D3 intake. This is supported by another study that featured a 10,000 IU supplementation schedule of vitamin D3 in patients with breast cancer [40]. Interestingly, in the study by Hohaus et al. [38] a weekly loading dose of 25,000 IU vitamin D3 was used for one group and perhaps more interesting was the fact that laboratory results showed that this supplementation schedule did not induce hypercalcemia. This is in accordance with other research that has indicated a dose of up to 10,000 IU of vitamin D for four months was safe in breast cancer patients and a loading dose of 20,000 IU in lung cancer patients was deemed safe as well in addition, single doses up to 200,000 IU of vitamin D have also been safe and effective suggesting a possible disruptive pathway between immunochemotherapy and vitamin D absorption [41]. Analysis by researchers in the study by Hohaus et al. [38] reported that 25(OH)D levels below 20 ng/mL had significantly lowered event-free survival rate.

## Synergistic Effect of Eicosapentaenoic Acid and Vitamin E

Eicosapentaenoic acid is a type of omega-3 fatty acid that has been known to lower the risk of heart disease. While many studies don't know the exact mechanism of doxorubicin-induced cardiomyopathy, many theories stem from the same idea, an influx of reactive oxygen species. Researchers in Egypt state that doxorubicin induces catalytic cycle disruption of topoisomerase 2B (as shown in Fig. 1.2) which results in the deuteriation and breaking of DNA strands in addition to mitochondrial dysfunction and cell death consistent with previous studies. The study by Fayez and Zaafan [42] suggested protective mechanisms of vitamin E were apparent through decreased cytochrome c and iNOS expression. Cytochrome c is a heme protein housed within and around the mitochondrial membranes responsible for the respiratory chain by transference of electrons between complex III and IV [43]. iNOS, short for Inducible nitric oxide synthase, is a contributor to pathogen killing, and has immune-regulatory effects, such as inhibiting T cell activity [44]. In the present study, pretreatment using eicosapentaenoic acid and vitamin E showed significant decrease of CK-MB activity compared to the control group [42]. The findings following the doxorubicin treatment

were consistent with the literature. Other studies have shown doxorubicin's ability to intercalate DNA which leads to the subsequent generation of reactive oxygen species [45, 46]. As demonstrated in Fig. 1.3, the generation of these species set off a domino effect resulting in conversions of membrane unsaturated fatty acids into lipid peroxides culminating in loss of cell membrane integrity and tissue injury [47]. Findings in the present study by Fayez and Zaafan [42] concluded with the discovery of the pathways leading to tissue injury caused by iNOS; toxicity of iNOS is caused by induction of peroxynitrites resulting after interaction between nitric acid and superoxide. Peroxy-nitrates have long been studied to cause energetic cell damage and death due to damage to the DNA through activation of poly-polymerase. Further analysis showed the apoptotic potential of doxorubicin which was observed by increased cytochrome c production in the heart tissue [48]. Free radical generation within membrane phospholipids of the mitochondria results in loss of mitochondrial membrane potential and causes leakage of cytochrome c in the cytosol resulting in apoptosis. Apoptosis occurs when the leaked cytochrome and apoptosis protease activation factor-1 forms a complex [49]. This complex finalizes after it activates initiator caspase-9 leading to apoptosis [50]. Pretreatment of vitamin E demonstrated significant decrease in cardiotoxic markers in cardiac and renal tissues. Vitamin E not only served as a cardioprotective agent but also as a potential anti-apoptotic agent against doxorubicin chemotherapy [42].

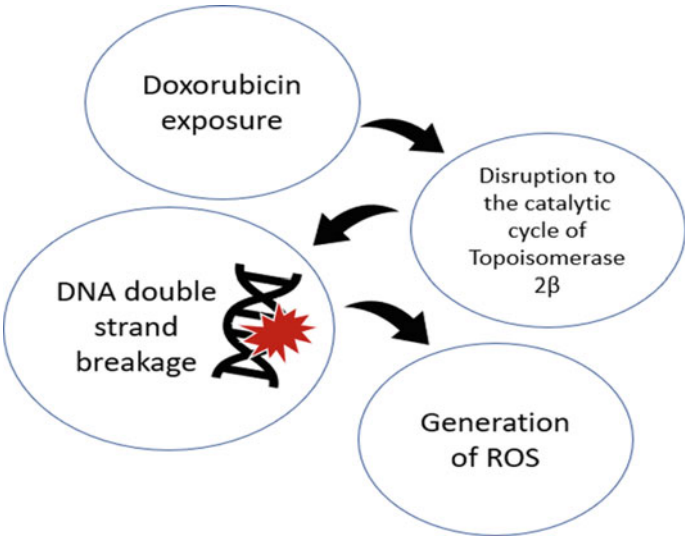


**Fig. 1.2** A schematic illustration of anthracycline exposure on DNA

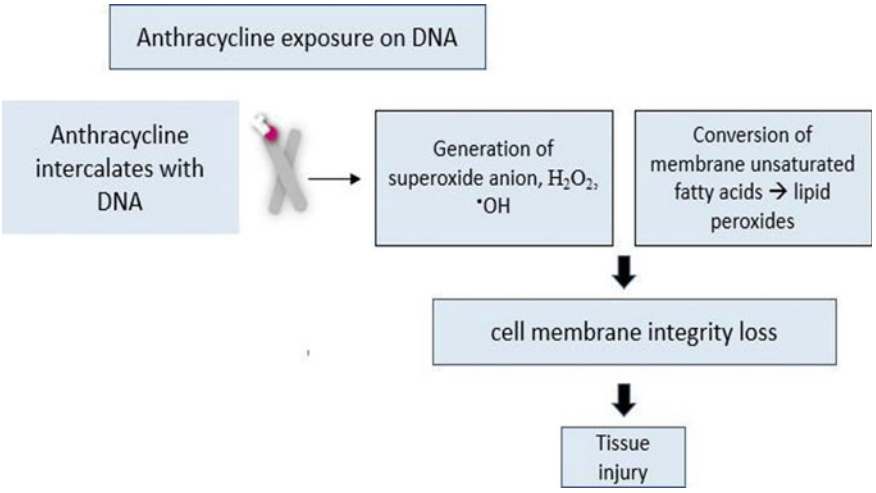


**Fig. 1.3** A simplified diagram proposing the doxorubicin exposure on the catalytic cycle leading to ROS production

## Synergistic Effect of Hesperidin and Vitamin E

In this study vitamin E was again used alongside hesperidin (HSP) for their presumed cardioprotective effects. The dosage of vitamin E was 100 mg/kg bodyweight two times during the week for three weeks [51]. The rats in the doxorubicin and HSP group had greater preservation of the myocardium with low myofibril loss. Histopathological analysis also showed less cytoplasmic vacuolization, less loss of myofibrils when compared to the doxorubicin group. There was also less infiltration of inflammatory cells compared to the doxorubicin group. The group that used vitamin E, HSP and doxorubicin, also had less loss of myofibrils and lower cytoplasmic vacuolization with no inflammation being the only difference between the two treatments. Oral administration of either HSP or vitamin E in single or combination doses decreased MDA levels indicating a cardioprotective effect demonstrated by antioxidant action.

In the present study, doxorubicin interfered with metabolism and biosynthesis of lipids which is significant due to the role lipids play in cardiovascular disease [52]. Cytochrome c also plays a part in apoptosis when it enters the mitochondria by lengthening the time calcium channels stay open in the sarcoplasmic reticulum [53]. This delay activates calcineurin with apoptosis occurring shortly after. In addition, oxidative stress activates Heat Shock Factor-1 leading to production of Heat Shock Protein ultimately increasing the number of pop-apoptotic proteins [54]. The reason oxidative stress is so harmful to the heart compared to other organs is due to its oxidative metabolism and its few antioxidant defenses [55].

## Vitamin E's Protective Effect on Cisplatin Induced Cardiotoxicity

Cisplatin, another chemotherapy agent, has also been well documented for its ability to cause cardiotoxicity. The pathways for cisplatin induced cardiotoxicity include reduction of ATP production and reduction in aerobic respiration as a result of the deterioration of cardiac muscle fibers [56]. Histopathological changes in previous studies have shown cisplatin induced cardiotoxicity manifest itself through cardiomyocyte necrosis, cytoplasmic vacuolization, and enlarged blood vessels [3].

In the present study, the cardioprotective effect of green tea extract alongside vitamin E were investigated. Vitamin E has been reported to be the most important antioxidant defense system due to its variety of biological functions. Enzymatic activity, gene regulation and inhibition of platelet aggression are all functions of vitamin E [57]. In other studies, vitamin E has shown to have a cardioprotective effect through its prevention of oxidative stress damage caused by fipronil, valproic acid, and cardiac malfunction due to diabetes and alloxan [58]. In the present study, a 30-day course of 100 mg/kg/day of vitamin E and 400 mg/kg/day of green tea extract were used in conjunction with cisplatin 7 mg/kg in 49 female albino mice. The second measure of the study was to examine the efficacy of cisplatin when used in conjunction with antioxidants. Troponin I, CPK and CK-MB were used as markers biomarkers for myocardial damage as they are the most sensitive to cardiotoxicity [59, 60]. Green tea extract showed a cardio-protective effect demonstrated by restoration of the previous biomarkers to normal levels after cisplatin intervention. Levels of MDA and an increase in GPx in the mice treated with GTE suggest levitation of oxidative stress through the scavenging of free radicals. The simultaneous use of vitamin E and GTE did not hinder the efficacy of cisplatin on anti-tumor activity [57]. Furthermore, vitamin E may be a great agent to use alongside when dealing with cisplatin induced cardiotoxicity for its ability to regulate caspase-independent pathways that lead towards apoptosis [61].

In a separate study, preventative activity of vitamin E and lipoic acid was investigated by Pillai et al. [62] particularly on doxorubicin induced oxidative stress. A 15 mg/kg dose of doxorubicin was used over two weeks in order to produce a cardiotoxic effect. The antioxidant properties of vitamin E have shown 50% decrease in mortality and dead cardiac tissue [63]. In addition, vitamin E has been shown to mitigate oxidative stress by trapping peroxyl radicals and ability to scavenge for free radicals [64]. In the present study, pretreatment with vitamin E increased GSH levels ($p < 0.01$) and decreased MDA levels ($p < 0.01$) compared to the DOX-treated group. LDH activity was also significantly changed ($p < 0.05$). Vitamin E observes a protective effect by serving as a radical scavenging agent, but it also serves as a trapping chain-breaking agent. The post-treatment of vitamin E did not increase GSH levels, but decreased MDA levels ($p < 0.01$) compared to DOX-treated groups and did not reduce LDH activity compared to the doxorubicin group. Post-treatment of lipoic acid and vitamin E caused the restoration of antioxidant markers, CAT, SOD, GPx, GST and G6PD in the heart tissue compared to the vehicle-treated group [62].

Researchers believe that influx of enzymatic activity could have been a mechanism caused by the myocardium in an effort to detoxify itself from the free radicals [65]. Levels of these enzyme were brought up to normal ranges indicating a beneficial potential effect of vitamin E and Lipoic acid. Further results from this study indicate that the biochemical changes coincide with histopathological changes in the myocardium. While the lipoic acid showed it has more of a curative effect, vitamin E demonstrated it could be used as a preventative and curative therapy indicating vitamin E as a better protector than lipoic acid [62].

A randomized control in-vivo study with rabbits produced severe cardiotoxicity evidenced by abnormal raised serum levels of cTn1, CK-MB, LDH, and grade 3 necrosis of heart tissue after single use of 12 mg/kg of doxorubicin [66]. Treatment yielded a dose response of cardiomyocyte cell death within two days after initial injection verified by histopathological reports. The second phase of the study focused on the cardioprotective effects of vitamin E as a-tocopherol administered as 200 mg/kg 10 days before doxorubicin exposure. LDH, CK-MB, and cTn1 were all significantly reduced ($p < 0.000$) histological changes were also comparable with the previous figures and also produced statistically significant changes. This study found quantitative estimation and dose responses that support the work of previous studies.

## Conclusion and Discussion

The findings prove that there is a strong reason to continue the research into the use of agents of cardio-protection like vitamin D and E. These agents have been successfully used in some studies as part of adjuvant therapy on individuals being treated for cancer.

Usage of antioxidant fat soluble vitamins have shown their effectiveness in bringing markers of cardiotoxicity to normal levels in some studies and have also shown their ability to ameliorate effects of reactive oxygen species as a result of various chemotherapies. These studies open the possibilities into the investigation of other protectors of cardiotoxicity, cytotoxicity, nephrotoxicity, etc. that could have real world clinical benefits.

Chemotherapy treatments are not the only treatments out there that cause cardiotoxicity or any type of toxicity in the human body likewise vitamins D and E are not the only agents that have been studied for their potential cardioprotective effect. This manuscript touches on a couple cardioprotective agents and one example of cardiotoxicity which is anti-cancer drug induced cardiotoxicity. There exist other medical interventions and illnesses that have been known to cause cardiotoxicity, cytotoxicity, nephrotoxicity, etc. and other protectors of these toxicities have also been studied but have yet to be fully understood. The findings discussed in this manuscript will hopefully be the beginning of what is yet to be explored in the realm of cardio-oncology, nutritional science, and all the other related scientific disciplines

regarding how modern medicine deals with all aspects of disease from prevention, intervention, and rehabilitation.

## Strengths and Limitations

The strength of this manuscript is that it is supported by peer reviewed work of many minds who have dedicated their lives to the fields of oncology and the effects of anti-cancer drug induced toxicity. The limitations are that many human studies are very new, especially studies that have recently discovered novel mechanisms involved in cardiotoxic and cardioprotective pathways. Human trials involving the use of fat-soluble vitamins during adjuvant therapy are limited and many of them have reported a lack of funding. There is also concern that antioxidant agents of cardio protection like Vitamin D and E may have a harmful effect on the anti-cancer drug's ability to successfully target tumor growth. This is a sizable worry since if true, could hinder the efficacy of tumor destroying drugs and result in less than favorable effects in prognosis.

**Acknowledgements** Our sincere thanks to Ms. Gurnoor Kaur, a diligent high school student, for the formatting of this manuscript in APA 7th edition, ensuring that the document adhered to the required formatting guidelines.

**Conflict of Interest** The authors declare no conflict of interest.

## References

1. Avila MS, Siqueira SRR, Ferreira SMA, Bocchi EA (2019) Prevention and treatment of chemotherapy-induced cardiotoxicity. Methodist DeBakey Cardiovasc J 15(4):267–273. https://doi.org/10.14797/mdcj-15-4-267
2. Lamberti M, Giovane G, Garzillo EM, Avino F, Feola A, Porto S, Tombolini V, Di Domenico M (2014) Animal models in studies of cardiotoxicity side effects from antiblastic drugs in patients and occupational exposed workers. Biomed Res Int 2014:240642. https://doi.org/10.1155/2014/240642
3. Florescu M, Cinteza M, Vinereanu D (2013) Chemotherapy-induced Cardiotoxicity. Maedica 8(1):59–67
4. Rhodes JM, Barrientos JC (2020) Chemotherapy-free frontline therapy for CLL: is it worth it? Hematol Am Soc Hematol Educ Prog 2020(1):24–32. https://doi.org/10.1182/hematology.2020000085
5. Feijen EA, Leisenring WM, Stratton KL, Ness KK, van der Pal HJ, van Dalen EC, Armstrong GT, Aune GJ, Green DM, Hudson MM, Loonen J, Oeffinger KC, Robison LL, Yasui Y, Kremer LC, Chow EJ (2019) Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. JAMA Oncol 5(6):864. https://doi.org/10.1001/jamaoncol.2018.6634
6. Gianni L, Herman EH, Lipshultz SE, Minotti G, Sarvazyan N, Sawyer DB (2008) Anthracycline cardiotoxicity: from bench to bedside. J Clin Oncol 26(22):3777–3784. https://doi.org/10.1200/JCO.2007.14.9401

7. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H (2021) Vitamin D and cardiovascular health. Clin Nutr (Edinb, Scotland) 40(5):2946–2957. https://doi.org/10.1016/j.clnu.2020.12.025
8. Lee KJ, Wright G, Bryant H, Wiggins LA, Dal Zotto VL, Schuler M, Malozzi C, Cohen MV, Gassman NR (2021) Cytoprotective effect of vitamin D on doxorubicin-induced cardiac toxicity in triple negative breast cancer. Int J Mol Sci 22(14):7439. https://doi.org/10.3390/ijms22147439
9. Hrelia S, Fiorentini D, Maraldi T, Angeloni C, Bordoni A, Biagi PL, Hakim G (2002) Doxorubicin induces early lipid peroxidation associated with changes in glucose transport in cultured cardiomyocytes. Biochim Biophys Acta (BBA) Biomemb 1567:150–156. https://doi.org/10.1016/s0005-2736(02)00612-0
10. Carrasco R, Castillo RL, Gormaz JG, Carrillo M, Thavendiranathan P (2021) Role of oxidative stress in the mechanisms of anthracycline-induced cardiotoxicity: effects of preventive strategies. Oxid Med Cell Longev 2021:8863789. https://doi.org/10.1155/2021/8863789
11. Rocca C, De Francesco EM, Pasqua T, Granieri MC, De Bartolo A, Gallo Cantafio ME, Muoio MG, Gentile M, Neri A, Angelone T, Viglietto G, Amodio N (2022) Mitochondrial determinants of anti-cancer drug-induced cardiotoxicity. Biomedicines 10(3):520. https://doi.org/10.3390/biomedicines10030520
12. Jiang X, Li L, Ying Z, Pan C, Huang S, Li L, Dai M, Yan B, Li M, Jiang H, Chen S, Zhang Z, Wang X (2016) A small molecule that protects the integrity of the electron transfer chain blocks the mitochondrial apoptotic pathway. Mol Cell 63(2):229–239. https://doi.org/10.1016/j.molcel.2016.06.016
13. Diaz-Vegas A, Sanchez-Aguilera P, Krycer JR, Morales PE, Monsalves-Alvarez M, Cifuentes M, Rothermel BA, Lavandero S (2020) Is mitochondrial dysfunction a common root of noncommunicable chronic diseases? Endocrine Rev 41(3):bnaa005. https://doi.org/10.1210/endrev/bnaa005
14. Volkova M, Russell R (2011) Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Bentham Sci 7(4):214–220. https://doi.org/10.2174/157340311799960645
15. Fox CA, Romenskaia I, Dagda RK, Ryan RO (2022) Cardiolipin nanodisks confer protection against doxorubicin-induced mitochondrial dysfunction. Biochim Biophys Acta (BBA) Biomemb 1864(10):183984. https://doi.org/10.1016/j.bbamem.2022.183984
16. Lima AR, Santos L, Correia M, Soares P, Sobrinho-Simões M, Melo M, Máximo V (2018) Dynamin-related protein 1 at the crossroads of cancer. Genes 9(2):115. https://doi.org/10.3390/genes9020115
17. Ko AR, Hyun HW, Min SJ, Kim JE (2016) The differential DRP1 phosphorylation and mitochondrial dynamics in the regional specific astroglial death induced by status epilepticus. Front Cell Neurosci 10:124. https://doi.org/10.3389/fncel.2016.00124
18. Chang YW, Weng HY, Tsai SF, Fan FS (2022) Disclosing an in-frame deletion of the titin gene as the possible predisposing factor of anthracycline-induced cardiomyopathy: a case report. Int J Mol Sci 23(16):9261. https://doi.org/10.3390/ijms23169261
19. Herzog W (2018) The multiple roles of titin in muscle contraction and force production. Biophys Rev 10(4):1187–1199. https://doi.org/10.1007/s12551-017-0395-y
20. Chen B, Zhong L, Roush SF, Pentassuglia L, Peng X, Samaras S, Davidson JM, Sawyer DB, Lim CC (2012) Disruption of a GATA4/Ankrd1 signaling axis in cardiomyocytes leads to sarcomere disarray: implications for anthracycline cardiomyopathy. PLoS ONE 7(4):e35743. https://doi.org/10.1371/journal.pone.0035743
21. Chen L, Holder R, Porter C, Shah Z (2021) Vitamin D3 attenuates doxorubicin-induced senescence of human aortic endothelial cells by upregulation of IL-10 via the pAMPKα/Sirt1/Foxo3a signaling pathway. PLoS ONE 16(6):e0252816. https://doi.org/10.1371/journal.pone.0252816
22. Qiu M, Shu H, Li L, Shen Y, Tian Y, Ji Y, Sun W, Lu Y, Kong X (2022) Interleukin 10 attenuates angiotensin II-induced aortic remodelling by inhibiting oxidative stress-induced activation of the vascular p38 and NF-κB pathways. Oxid Med Cell Longev 2022:8244497. https://doi.org/10.1155/2022/8244497