Mohammad Fahad Ullah · Aamir Ahmad
Editors

Critical Dietary Factors in Cancer Chemoprevention

Springer

Critical Dietary Factors in Cancer Chemoprevention

Mohammad Fahad Ullah • Aamir Ahmad
Editors

Critical Dietary Factors in Cancer Chemoprevention

Springer

Editors
Mohammad Fahad Ullah
Prince Fahd Research Chair
Department of Medical Laboratory Technology
FAMS, University of Tabuk
Tabuk, Saudi Arabia

Aamir Ahmad
Department of Pathology
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan
USA

ISBN 978-3-319-21460-3 ISBN 978-3-319-21461-0 (eBook)
DOI 10.1007/978-3-319-21461-0

Library of Congress Control Number: 2015952214

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Foreword

This book entitled "Critical dietary factors in cancer chemoprevention" is a comprehensive attempt to highlight novel opportunities for the prevention of neoplastic diseases by dietary means. Recently emerging evidence has revealed that long-term lifestyle factors including dietary habits significantly influence cancer development, progression, and response to therapy. Modification of dietary habits to include dietary factors with evidence of chemopreventive properties via the modulation of intracellular signaling pathways as regular components of diet has thus been conceived to be a potential strategy to lower the risk and burden of cancer incidence. Furthermore, these dietary factors also provide leads to potent therapeutic drugs with elevated margins of safety. This book provides an update on contemporary research in this field with an impressive group of authors. A unique feature of the book is that along with regular chapters, there are expert opinions from renowned authors, a strategy that enhances the impact of the knowledge and information emanating from this compilation.

I commend the editors, Dr. Mohammad Fahad Ullah and Dr. Aamir Ahmad and all the contributors, for this significant piece of work that encourages the engagement of dietary factors as an effective paradigm in cancer prevention.

Knoxville, TN, USA — Hildegard M. Schuller, D.V.M., Ph.D

Preface

The success of scientific research on the ladder of validation is perfected when the idea traverses the untrodden path and delivers the desired benefit to the community of people. This book "Critical dietary factors in cancer chemoprevention" is an attempt of archiving a few such ideas in scientific and public domain. We commend Springer Publishers in providing the foundation for this endeavor and entrusting us with the task of managing and editing the current volume of the compilation that we present before the audience.

Precisely, the volume contains two sections. Section I introduces the importance of the topic of this book through the opinion of three renowned experts who have immensely contributed to the area of dietary factors in prevention of cancer for more than four decades. This is followed by Section II which has 15 chapters that are intended to highlight the significance of dietary factors in the premises of cancer chemoprevention as part of prophylactic, therapeutic, or adjuvant interventions.

Section I: Curcumin, a constituent of turmeric which is used as spice in food and anti-inflammatory agent in traditional medicines, has been known for long to possess anticancer properties. In the first expert opinion, Dr. Sarkar provides an update on a novel synthetic analogue of curcumin, CDF, with regard to its enhanced efficacy against cancer. This reflects that the dietary agents have the potential to not only provide preventive strategy as part of regular consumption but also have the potential to act as lead compound for the development of therapeutic interventions. The second opinion comes from Dr. Mukhtar, which advocates the synergism of bioactive compounds as a cocktail in the development of personalized approach to cancer chemoprevention. Dr. Hadi contributes the third expert opinion whereon he explains the delicate balance of the contrasting properties of bioactive molecules acting as both the antioxidants and prooxidants and how these could be utilized in their potential against cancer.

Section II: Chapter "Phytocomplexity: the key to rational chemoprevention" provides an excellent presentation of a concept that links the significance of phytocomplexity of whole fruits or vegetables in harvesting the desired chemopreventive efficacy in cancer prevention. Chapter "The ketogenic diet as an adjuvant therapy for brain tumors and other cancers" precisely deals with metabolic therapy where the authors suggest the application of ketogenic diet as an adjuvant therapy in starving the cancer cells of energy. Chapter "The role of organosulfur compounds derived from Allium vegetables in cancer prevention and therapy" explores the anticancer potential of bioactive compounds of organosulfur nature, emerging as a promising cancer chemopreventive strategy. Chapter "Epigenetic Impact of Bioactive Dietary Compounds in Cancer Chemoprevention" deliberates the influence of dietary factors in reversing the epigenetic events following the process of neoplastic transformation. Chapters "Potential for sesame seed-derived factors to prevent colorectal cancer" and "Progress in the development of black seed derived anticancer agents" present an overview of the anticancer potential of the bioactive constituents of sesame seed and black seed, respectively, and provide mechanism-based insights. Chapters "Soy isoflavones in the breast cancer risk: from preclinical findings to clinical strategy" and "Pharmacological role of dietary polyphenols in prostate cancer chemoprevention" focus on certain dietary agents with critical value in the prevention of breast cancer and prostate cancer, respectively. Chapter "Effects of garcinol from kokum (Garcinia indica) on the prevention and treatment of cancer" gives an account of nutraceutical garcinol and its chemopreventive efficacy against cancer. Chapters "Modulation of key signaling pathways in cancer cells by dietary factors" and "Pivotal role of chemokine receptor signaling axis and natural bioactive chemopreventive agents in metastasis of breast cancer" demonstrate the complex nature of cellular signaling in cancer cells and the ability of dietary compounds to interfere with these pathways. Chapter "Dietary factors may influence the clinical outcome of chemotherapy in cancer multidrug resistance" discusses the current interest in dietary molecules with respect to their potential role in addressing the drug resistance in cancer. Chapter "The role of energy balance in cancer prevention" points to the need of energy-balanced dietary intake in reducing the risk of cancer. Chapter "Dietary/environmental factors and breast cancer" reviews the significance of dietary fats and Mediterranean diet in relation to breast cancer risk. Finally, chapter "Probiotic bacteria in patients treated with chemotherapy and radiation therapy" addresses the emerging role of probiotics in the management of toxic responses associated with chemo- and radiation therapy in cancer patients.

We express our gratitude to all the authors for valuable contribution from around the globe. It is their willingness to share their onerous experiences which has empowered us to bring forth this piece of scientific literature. We appreciate the support of Dr. Beatrice Menz (Senior Editor, Springer Basel) for working out the procedural framework of our book proposal. Fortunately, we had Ms. Kay Stoll (Springer Production), as an excellent project coordinator, who provided the basic

skeleton of strength that is required for any attractive and meaningful academic production. We are indeed honored to have Prof. Hildeguard M. Schuller introducing the substance of the book in the foreword.

Lastly, we wish that the audience will like the contents of this book and it will take us a step forward in understanding the critical nature of lifestyle issues vis–àvis dietary habits in reducing the risk of chronic diseases such as cancer.

Tabuk, Saudi Arabia — Mohammad Fahad Ullah
Detroit, MI, USA — Aamir Ahmad

Book Description

The poor survival statistics of fatal cancer diseases highlight the need for multiple alternative treatment options along with effective prophylactic strategies. Worldwide geographical variation in cancer incidence indicates a correlation between dietary habits and cancer risk. Moreover, an impressive embodiment of evidence supports the concept that dietary factors are key modulators of cancer. A number of action mechanisms have been reported for these dietary factors to retard, block, or reverse carcinogenesis.

Lifestyle issues including poor dietary habits are major impediment in the prevention of cancer. In addition, in recent past there has been an unprecedented surge of evidence implicating a large number of dietary agents in the prevention of cancer. A well-orchestrated campaign is thus required to highlight the clinical relevance of these factors in diet among the global population. The four distinct advantages of these agents are their diverse structure, pleiotropic action mechanism to simultaneously influence multiple targets, significantly lower toxicity, and selective killing of cancer cells (by certain dietary agents). Most of these agents are derived from fruits, vegetables, and grains and can easily be incorporated as routine dietary regimen. Further, their clinical potential might also be exploited as adjuvant therapy in the management of the disease along with conventional treatment to enhance the clinical outcome.

This book presents a *prophylactic approach* to primary prevention of cancer disease by highlighting the translational potential of diet-derived factors from epidemiological, laboratory, and clinical studies, as *prevention strategy* in normal/risk populations through routine inclusion of specific dietary regimens and as *therapeutic strategy* for better management through adjuvant interventions in cancer treatment.

The volume shares the experiences of highly reputed experts working in the area of dietary agents and cancer chemoprevention to promote the significance of dietary factors and elevate the dietary habits as an elite priority for containing the cancer disease.

Contents

Part I Expert Opinion

Updates on the Promising Anticancer Activity of CDF, a Synthetic Curcumin Analogue 3
Kevin R. Ginnebaugh, Aamir Ahmad, and Fazlul H. Sarkar

Prostate Cancer Chemoprevention by Dietary Agents: Advocating a Personalized Multi-agent Approach 13
Vaqar Mustafa Adhami and Hasan Mukhtar

Making Sense of Antioxidant–Pro-oxidant Conundrum in Anticancer Research 31
SM Hadi and Mohd Farhan

Part II Elements of Dietary Approaches to Cancer Chemoprevention

Phytocomplexity: The Key to Rational Chemoprevention 39
Sushma R. Gundala, M. Hope Robinson, and Ritu Aneja

The Ketogenic Diet as an Adjuvant Therapy for Brain Tumors and Other Cancers 89
Kenneth S. Brooks, Eric C. Woolf, and Adrienne C. Scheck

The Role of Organosulfur Compounds Derived From *Allium* Vegetables in Cancer Prevention and Therapy 111
Ajay Bommareddy, Adam L. VanWert, Dan F. McCune, Sarah L. Brozena, Zbigniew Witczak, and Shivendra V. Singh

Epigenetic Impact of Bioactive Dietary Compounds in Cancer Chemoprevention 153
Gordana Supic, Darja Wagner, and Zvonko Magic

Potential for Sesame Seed-Derived Factors to Prevent Colorectal Cancer 183
Shingo Miyamoto, Gen Fujii, Masami Komiya, Masaru Terasaki, and Michihiro Mutoh

Progress in the Development of Black Seed-Derived Anticancer Agents 199
Irfana Muqbil and Ramzi M. Mohammad

Soy Isoflavones in the Breast Cancer Risk: From Preclinical Findings to Clinical Strategy 213
P. Kubatka, J. Mojžiš, M. Pilátová, M. Péč, and P. Kruzliak

Pharmacological Role of Dietary Polyphenols in Prostate Cancer Chemoprevention 239
Sebastiano Cimino, Giorgio Ivan Russo, Giulio Reale, Daniele Urzì, Tommaso Castelli, Vincenzo Favilla, and Giuseppe Morgia

Effects of Garcinol from Kokum (*Garcinia indica*) on the Prevention and Treatment of Cancer 253
Bernhard Biersack

Modulation of Key Signaling Pathways in Cancer Cells by Dietary Factors 273
Amrah Ali and Aamir Ahmad

Pivotal Role of Chemokine Receptor Signaling Axis and Natural Bioactive Chemopreventive Agents in Metastasis of Breast Cancer 285
Sanjeev Banerjee, Shivani B Paruthy, Paul R Rajamani, and Bin Bao

Dietary Factors May Influence the Clinical Outcome of Chemotherapy in Cancer Multidrug Resistance 307
Mohammad Fahad Ullah, Showket H. Bhat, and Faisel M. Abuduhier

The Role of Energy Balance in Cancer Prevention 321
Suzanne L. Doyle, Claire L. Donohoe, and John V. Reynolds

Dietary/Environmental Factors and Breast Cancer 339
Michel de Lorgeril and Patricia Salen

Probiotic Bacteria in Patients Treated with Chemotherapy and Radiation Therapy 353
Michal Mego, Sona Ciernikova, Martin Razus, Lubos Drgona, and Vladimir Zajac

About the Editors

Mohammad Fahad Ullah is an Assistant Professor of biochemistry in the Faculty of Applied Medical Sciences and a Research scientist at Prince Fahd Research Chair, University of Tabuk, Saudi Arabia. He received his academic degrees along with a gold medal in M.Sc. (biochemistry) from Aligarh Muslim University, India. Further he worked as a research associate at Experimental Oncology laboratory, Department of Biomedical and Diagnostic Sciences, University of Tennessee, USA, where he received an excellence in research award on studies related to cancer cell signaling in cellular and animal models of lung and pancreatic cancer. His research interest is in the field of novel plant- or diet-derived chemopreventive compounds for assessing the mechanism of action and examining their translational potential. He is member of the editorial/reviewer board of a number of scientific journals.

Aamir Ahmad is a Research Scientist at the Wayne State University, Department of Pathology, and Barbara Ann Karmanos Cancer Institute, Detroit, MI. His research interests include elucidating novel targets for therapy in aggressive breast cancers with special focus on key signaling pathways and microRNA-mediated regulation of metastases and drug resistance. Dr. Ahmad has authored more than 120 scientific publications and also serves as a section editor for the journal PLOS One.

Part I
Expert Opinion

Updates on the Promising Anticancer Activity of CDF, a Synthetic Curcumin Analogue

Kevin R. Ginnebaugh, Aamir Ahmad, and Fazlul H. Sarkar

Abstract In the last few decades we have witnessed an increased interest in nutraceuticals research for their putative use as anticancer therapeutics. A major drawback of nutraceuticals is their poor bioavailability. A few years back we synthesized a difluorinated analogue of curcumin, named CDF, which showed promise during our initial studies by being more bioavailable. This prompted us to investigate the anticancer mechanism(s) of this promising compound in detail, with the ultimate goal of taking this compound to the clinical setting. In this expert opinion, we provide a succinct overview of all the biological effects of CDF that we have discovered in the last few years. These include the ability of CDF to regulate epigenetic factors, miRNAs, and the cancer stem cell markers. Development and characterization of CDF is a good example of how natural chemical structures can be modified for better efficacy and activity against cancer cells, although such agents require further development for clinical studies.

1 Introduction

Cancer is a disease characterized by a few key events: division of cells containing mutations, unlimited replication potential, and invasion and growth of these cells in surrounding and distant organs through the assistance of the circulatory or

K.R. Ginnebaugh
Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, 740 HWCRC Bldg, 4100 John R. Street, Detroit, MI 48201, USA

A. Ahmad
Department of Pathology, Karmanos Cancer Institute, Wayne State University-740 HWCRC, Detroit, Michigan, USA

F.H. Sarkar, Ph.D. (✉)
Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, 740 HWCRC Bldg, 4100 John R. Street, Detroit, MI 48201, USA

Department of Oncology, Karmanos Cancer Institute, Wayne State University School of Medicine, 740 HWCRC Bldg, 4100 John R. Street, Detroit, MI 48201, USA
e-mail: fsarkar@med.wayne.edu

M.F. Ullah, A. Ahmad (eds.), *Critical Dietary Factors in Cancer Chemoprevention*,
DOI 10.1007/978-3-319-21461-0_1

lymphatic systems. These cells can arise through mutations accumulating due to the normal aging process and genetic predisposition or through the influence of environmental factors such as exposure to carcinogenic insults. In the year 2015, it has been predicted that 1,658,370 new cancer cases and 589,430 cancer deaths will occur in the United States alone (Siegel et al. 2015). Current drug and chemotherapy options contain many harmful side effects to the individual affected by the disease. Nutraceuticals, the therapeutic agents of natural origin, have shown promise to combat the harmful side effects of current treatment options. Nutraceuticals have been shown to help combat diseases like CVDs, obesity, GI tract disorders, as well as cancer (Gul et al. 2015). Nutraceuticals have been shown to have pleiotropic effects and the ability to target multiple cellular signaling pathways which has been one of the greatest attributes of natural agents, and is not achievable through current cancer therapeutics. Nutraceuticals have also been found to be effective in helping to resensitize drug-resistant cancers to conventional agents (Ahmad et al. 2015a). An example of the benefits found with nutraceuticals is in the chemoprevention of human cancers. For example, prostate cancer which typically impacts the aging population has been found to be heavily influenced by dietary habits (Syed et al. 2008). With increased dietary intake of chemopreventive substances, one could hope to possibly prevent or slow down the development and progression of prostate cancer. Pleiotropic effects of nutraceuticals have been found to be active in the regulation of miRNA–cancer stem cells nexus among many other biological effects of nutraceuticals (Ahmad et al. 2014). In the subsequent section, we will limit our discussion on curcumin and its analogues.

Curcumin, the active chemical found in the spice turmeric, is a yellow substance belonging to the polyphenols superfamily. Curcumin, through a variety of mechanisms, has been shown to exhibit anticancer effects (Shanmugam et al. 2015). Anticancer effects of curcumin are predominantly mediated through its negative regulation of growth factors, inflammatory cytokines, protein kinases, oncogenic molecules, and transcription factors (Shanmugam et al. 2015). One example of how this nutraceutical targets these processes was reported in bladder cancer, where it functions to increase miR-203 expression, ultimately decreasing levels of Akt2 and Src which were found to be elevated in untreated bladder cancer (Ahmad et al. 2014). Two other signaling pathways which have been associated with cancer development and progression are NF-kB and STAT3. Curcumin has been shown to inhibit these pathways resulting in the inhibition of either the development cancer and/or by inducing apoptosis of cancer cells (Vallianou et al. 2015). One of the reasons why curcumin has shown to be such a promising area of research is due to its documented lack of systemic toxicity. Multiple studies on a variety of mammals such as monkeys, horses, and rodents have provided great evidence in support of its superior safety profile and lack of systemic toxicity to the organism(s) (Howells et al. 2014). This has led to recent clinical trials with disappointing outcome in general. Besides cancer, curcumin is also being researched in pro-inflammatory diseases including cardiovascular disease, arthritis, ulcerative diseases, and Crohn's disease (Gupta et al. 2013a). Given orally, curcumin has been found to inhibit cancers including lung, skin, head and neck, oral, and many others in preclinical models (Gupta et al. 2013b; Rahmani et al. 2014). Sustained tissue concentrations

have been reached using subcutaneous delivery, including one instance where mice liver was shown to contain curcumin a month after treatment (Gupta et al. 2013b). Despite all of these proven benefits of curcumin, curcumin has failed in clinical settings. This failure can be partly attributed to curcumin's poor bioavailability. When a subject takes an oral dose of curcumin, it undergoes complex metabolism rendering it inactive or rapid clearance via enzymatic processes. One way the bioavailability of curcumin could be improved is through generation of newly synthesized curcumin analogs; one such analogue is CDF (difluorinated curcumin) as described by our group (Padhye et al. 2009a, b). CDF has also been found to cause a marked decrease in NF-kB transcription and shows more pronounced effect at lower doses when compared with curcumin (Padhye et al. 2010). CDF also showed increased bioavailability after oral administration which was due to multiple beneficial attributes of CDF (Sarkar et al. 2010). In addition to studies on CDF, we have also synthesized CDF with β-cyclodextrin and this formulation was observed to enhance CDF's delivery to the pancreas, thus showcasing its improved bioavailability (Dandawate et al. 2012). In the following sections, we will summarize the various signaling pathways, factors, and therapeutic targets that are affected by CDF. Research investigations over past several years in our laboratory have focused on elucidating the mechanism(s) of antitumor activity of CDF, and thus we will provide a brief overview of this promising anticancer compound in this expert review.

2 Signaling Pathways

2.1 AR/TMPRSS2-ERG/Wnt Signaling

In patients suffering from prostate cancer, the progression to castrate-resistant prostate cancer (CRPC) after anti-androgen ablation therapy is driven in part by deregulated functions of the androgen receptor (AR), which is required for sustained growth of CRPC cells. Our lab discovered that AR activation resulted in greater ERG expression through the fusion of TMPRSS2-ERG (Li et al. 2011). ERG overexpression was also linked to Wnt signaling activation (Wu et al. 2013). CDF was found to inhibit signal transduction of the AR/TMPRSS2-ERG/Wnt signaling pathways, inhibiting invasion of prostate cancer cells and cellular proliferation. CDF was also linked to increased cancer cell apoptosis, underlying its potential application in the fight against prostate cancer (Li et al. 2011).

2.2 NF-κB Signaling

The role of NF-κB in the progression of human cancers has been well documented (Ben-Neriah and Karin 2011; Sarkar and Li 2008; Sarkar et al. 2008; Bao

et al. 2012a; Ahmad et al. 2013; Tkach et al. 2014). Our lab looked at the levels of expression of NF-κB in pancreatic cancer cells BxPC-3 and MIAPaCa-epithelial (E)/mesenchymal(M) phenotypic cells (Ali et al. 2010). After the cells treated with CDF for 72 h, we reported a decrease in the DNA binding activity of NF-kB when compared to untreated cells. Such decrease in NF-κB activity was correlated with increased apoptotic cell death as well as resulted in the inhibition of cancer-associated signaling pathways. CDF's proven greater retention and bioavailability compared to curcumin have also been established in our lab. We have demonstrated that the inhibition of the DNA binding activity of NF-kB by CDF was far superior compared to curcumin (Padhye et al. 2009b).

3 The Biological Significance of microRNAs

The emerging role of small noncoding microRNAs (miRNAs) in human diseases, especially in cancer, is non-refutable (Xue et al. 2014; Hata and Lieberman 2015; Vidigal and Ventura 2015; Chan et al. 2015). Our own laboratory has been on the forefront of studies aimed at elucidating the mechanistic involvement of several miRNAs in human cancers which can serve as the basis of targeted anticancer therapies (Ali et al. 2011; Sethi et al. 2013, 2014; Ahmad et al. 2014). In the next few subsections, we will briefly discuss our published studies that documented deregulation of miRNAs by CDF.

3.1 miR-21 and miR-210

miR-21 is a miRNA that has been found to be associated with several cancers (Sheedy 2015; Pan et al. 2010; Gao et al. 2012; Liu et al. 2014; Fu et al. 2011). Being an oncogenic miRNA, its major targets are tumor suppressor genes, and it has been found to be expressed at higher levels in cancer cells than normal cells, potentially making it a biomarker for cancer diagnosis and prognosis as well as a target of the development of novel therapeutics. Upregulation of miR-21 has been found in colon cancer cells which could serve as a marker for potential recurrence of colon cancer in patients. PTEN, a target of miR-21, is a tumor suppressor gene responsible for the regulation of self-renewal in stem cells. Increased expression of PTEN has been found to be associated with decreased metastatic potential of tumor cells. Increased expression of miR-21 resulted in decreased expression of PTEN which was in part responsible for increased invasiveness and metastatic potential of colon cancer cells. Aggressive colon as well as pancreatic cancer cells treated with CDF showed re-expression of PTEN, which was mediated through downregulation in the expression of miR-21 (Roy et al. 2013; Bao et al. 2011; Ali et al. 2010).

Hypoxia causes prostate and pancreatic cancer cells to become much more aggressive. This aggression is in part due to increased expression of miRNAs,

such as miR-21 and miR-210, and activation of many transcription factors. Increased expression of miR-21 has been found to be associated with increased mesenchymal transition of tumor cells, and upon treatment with CDF, resulted in decreased expression of these pro-metastatic genes which led to decreased cell proliferation and invasion, as well as increased apoptosis (Bao et al. 2012b, c).

Another consequence of miR-21 in pancreatic cancer is increased Ras GTPase activity (Ali et al. 2012). Such increased Ras activity causes increases in tumor aggressiveness and increased cell proliferation. CDF, when introduced in vitro to pancreatic cancer cells, showed decreased miR-21 levels which was correlated with decreased Ras activity.

3.2 miR-200, let-7s, miR-101, and miR-143

In addition to being regulated by miR-21, as discussed above, increased Ras GTPase activity in pancreatic cancer cells is also regulated by let-7s and miR-143. Forced re-expression of these miRNAs in pancreatic cancer cells showed marked reduction in GTPase activity as analyzed by western blot analysis (Ali et al. 2012). CDF treatment of pancreatic cancer cells resulted in decreased cell survival, invasion cell migration, and cancer stem cell function as well as decreased drug resistance. These decreases in tumor aggressiveness characteristics can be attributed to increased levels in the expression of tumor suppressor miRNAs such as miR-101, miR-143, miR-200, and the let-7 family, all of which were found to be upregulated by CDF treatment (Bao et al. 2011, 2012c, d; Ali et al. 2010, 2012).

Let-7 and miR-101 are also associated with the regulation of histone methyltransferase EZH2. EZH2 is a regulator of cell survival, proliferation, and cancer stem cell function. Due to its increased level of expression in human cancers, such as pancreatic cancer, it is associated with increased aggressive behavior of tumors. Let-7 and miR-101 when expressed in high concentration were able to inhibit these effects of EZH2. CDF positively regulates let-7 and miR-101, thus resulting in decreased pancreatic cancer cell survival, invasiveness, and cancer stem cell function by decreasing EZH2 expression (Bao et al. 2012d).

3.3 miR-874

In a recent study (Ahmad et al. 2015b), we compared the direct effect of curcumin vs. CDF on the inhibition of MMP-2 (matrix metalloproteinase-2). We focused on MMP-2 because of its reported role in invasion and metastasis of cancer cells. Through a number of approaches such as *in silico* docking, gelatin zymography, invasion assays, and ELISA, we observed a significantly more inhibition of MMP-2 by CDF, compared to its inhibition by curcumin in lung cancer cells (A549 and H1299 cells). As a mechanism, we noted an upregulation of miR-874, an MMP-2

Table 1 miRNA targets of CDF

miRNA	Up/downregulated by CDF	Reference(s)
Let-7s	Upregulated	Ali et al. (2012) and Bao et al. (2012d)
miR-21	Downregulated	Roy et al. (2013), Bao et al. (2011, 2012b, c) and Ali et al. (2010, 2012)
miR-101	Upregulated	Bao et al. (2012d)
miR-143	Upregulated	Ali et al. (2012)
miR-200	Upregulated	Bao et al. (2011, 2012d) and Ali et al. (2010)
miR-210	Downregulated	Bao et al. (2012c)
miR-874	Upregulated	Ahmad et al. (2015b)

targeting miRNA, by CDF. Thus, CDF induced the expression of miR-874 which resulted in the downregulation of its target MMP-2. These results provided another mechanism by which CDF could exert its anticancer effects.

In summary, detailed investigations reported by our laboratory have established a miRNA-modulating effect of CDF, which defines an important mechanism of action of CDF for the inhibition of cell growth of human cancer cells (Table 1). As discussed in this section, regulation of different miRNAs by CDF has been demonstrated in colon, prostate, pancreatic, as well as lung cancer cells. Given the versatility of CDF function, it will not be surprising to observe such effects of CDF in other cancer models as well, an idea that is under active investigation in our laboratory.

4 Cancer Stem Cells

Cancer stem cells, due to their resistance to chemotherapy, are currently thought to be the cause of recurrence in all human cancers. In order to fight cancer, these cells need to be eradicated. In a study conducted in colon cancer model (Kanwar et al. 2011), treatment with CDF resulted in increased levels of apoptosis and decreased cellular growth. CDF, due to its ability to downregulate cancer stem cell properties and induce apoptosis, along with conventional chemotherapeutics could prove to be effective in reducing reemergence of tumor growth.

Under hypoxic conditions, maintenance of cancer stem cell functions occurs through hypoxia-inducing factor (HIF) signaling (Bao et al. 2012c). In mouse models, in response to hypoxia-induced aggressiveness, cancer stem cell signatures were decreased in pancreatic cancer after administration of CDF. Moreover, CDF downregulated the expression of CD44 and EpCAM cell surface markers, which are usually the hallmark of cancer stem cells (Kanwar et al. 2011). One way by which CDF targets cancer stem cells is that it inhibits the formation of pancreatospheres. Inhibiting the formation of pancreatospheres was consistent

with gradual decrease in the expression of CD44 and EpCAM cancer stem cell markers, which led to the inhibition of tumor growth (Bao et al. 2011).

5 Sensitization of Drug-Resistant Cells by CDF

Drug resistance is a major clinical problem. CDF has been found to be effective against chemotherapy-resistant colorectal cancer cells which was in part due to the ability of CDF to restore the levels of tumor suppressor PTEN (Roy et al. 2013). PTEN is an anti-metastatic/tumor suppressing protein, responsible for self-renewal of stem cells. This restoration of tumor suppressor PTEN was accompanied by downregulation of miR-21 which is typically increased during drug resistance due to the inhibition in the expression of tumor suppressor genes.

CDF was also able to resensitize pancreatic cancer cells to gemcitabine (Ali et al. 2010). Gemcitabine resistance appears to be in part associated with downregulation of miR-200 and increased miR-21 levels in pancreatic cancer cells. Treatment of pancreatic cancer cells with CDF led to increased expression of miR-200 and decreased expression of miR-21 which resulted in the gemcitabine-resistant cells sensitive to gemcitabine, and thus induced cell growth inhibition and increased apoptotic cell death.

6 Epigenetics

EZH2 is an enzyme that is highly expressed in numerous human cancers. EZH2 uses epigenetic programming to regulate cancer stem cell function, proliferation of cancer cells, and cellular survival. Treating pancreatic cancer cells with CDF, we were able to decrease the expression of EZH2; CDF also seemed to increase the expression of tumor suppressor miRNAs, including let-7s, miR-101, and miR-200 which were previously discussed. By targeting the EZH2-miRNA regulatory circuit, CDF inhibited pancreatic tumor growth and decreased the aggressiveness of tumors (Bao et al. 2012d).

7 Conclusions and Perspectives

Curcumin has been widely investigated and has been proven to be a potent anti-inflammatory, as well as an antioxidant agent with antitumor activity in preclinical studies. However, it has been shown to possess low bioavailability, which has rendered it clinically unacceptable. The bioavailability concerns led us to synthesize CDF among many other analogues that we had synthesized. We were able to demonstrate that CDF accumulates at a greater concentration in blood and in many

other organs, for example, the pancreas. It has now been well accepted that cancer is difficult to treat which is, in part, due to deregulated expression of multiple signaling pathways supporting rapid cell proliferation and evasion of apoptosis. Therefore, cancer is a disease of multi-gene defects, and thus a multipronged approach is expected to be a better approach for the eradication of cancer. To that end, it is important to note that CDF is a multi-targeted agent whose antitumor activity is mediated through deregulation of a variety of signal transduction cascades including miRNAs, NF-κB, AR/TMPR552/Wnt signaling, epigenetic reprograming, and attenuating the many cellular attributes of cancer stem cells. Through these mechanisms, treatment of cancer cells with CDF causes cancer cells to undergo apoptosis, decrease their replicative potential, and also reduce "stemness" characteristics of cancer stem cells, thus resulting in the inhibition of tumor growth. Moreover, CDF could serve as a powerful agent for overcoming drug resistance, a major problem in cancer treatment. In addition, the superior bioavailability of CDF together with potential of its systemic nontoxic attributes could become clinically attractive for further development of CDF as a new anticancer drug for the treatment of human malignancies with better therapeutic outcome. In conclusion, CDF and other nutraceuticals or their synthetic analogues may open new horizon in the discovery of newer anticancer drugs toward achieving the goal to eradicate cancers.

References

Ahmad A, Biersack B, Li Y, Kong D, Bao B, Schobert R et al (2013) Targeted regulation of PI3K/Akt/mTOR/NF-kappaB signaling by indole compounds and their derivatives: mechanistic details and biological implications for cancer therapy. Anticancer Agents Med Chem 13(7): $32#1002–1013

Ahmad A, Li Y, Bao B, Kong D, Sarkar FH (2014) Epigenetic regulation of miRNA-cancer stem cells nexus by nutraceuticals. Mol Nutr Food Res 58(1):79–86. doi:10.1002/mnfr.201300528

Ahmad A, Ginnebaugh KR, Li Y, Padhye SB, Sarkar FH (2015a) Molecular targets of naturopathy in cancer research: bridge to modern medicine. Nutrients 7(1):321–334. doi:10.3390/nu7010321

Ahmad A, Sayed A, Ginnebaugh KR, Sharma V, Suri A, Saraph A et al (2015b) Molecular docking and inhibition of matrix metalloproteinase-2 by novel difluorinatedbenzylidene curcumin analog. Am J Transl Res 7(2):298–308

Ali S, Ahmad A, Banerjee S, Padhye S, Dominiak K, Schaffert JM et al (2010) Gemcitabine sensitivity can be induced in pancreatic cancer cells through modulation of miR-200 and miR-21 expression by curcumin or its analogue CDF. Cancer Res 70(9):3606–3617. doi:10.1158/0008-5472.CAN-09-4598

Ali AS, Ali S, Ahmad A, Bao B, Philip PA, Sarkar FH (2011) Expression of microRNAs: potential molecular link between obesity, diabetes and cancer. Obes Rev 12(12):1050–1062. doi:10.1111/j.1467-789X.2011.00906.x

Ali S, Ahmad A, Aboukameel A, Bao B, Padhye S, Philip PA et al (2012) Increased Ras GTPase activity is regulated by miRNAs that can be attenuated by CDF treatment in pancreatic cancer cells. Cancer Lett 319(2):173–181. doi:10.1016/j.canlet.2012.01.013

Bao B, Ali S, Kong D, Sarkar SH, Wang Z, Banerjee S et al (2011) Anti-tumor activity of a novel compound-CDF is mediated by regulating miR-21, miR-200, and PTEN in pancreatic cancer. PLoS One 6(3):e17850. doi:10.1371/journal.pone.0017850

Bao B, Thakur A, Li Y, Ahmad A, Azmi AS, Banerjee S et al (2012a) The immunological contribution of NF-kappaB within the tumor microenvironment: a potential protective role of zinc as an anti-tumor agent. Biochim Biophys Acta 1825(2):160–172. doi:10.1016/j.bbcan.2011.11.002

Bao B, Ahmad A, Kong D, Ali S, Azmi AS, Li Y et al (2012b) Hypoxia induced aggressiveness of prostate cancer cells is linked with deregulated expression of VEGF, IL-6 and miRNAs that are attenuated by CDF. PLoS One 7(8):e43726. doi:10.1371/journal.pone.0043726

Bao B, Ali S, Ahmad A, Azmi AS, Li Y, Banerjee S et al (2012c) Hypoxia-induced aggressiveness of pancreatic cancer cells is due to increased expression of VEGF, IL-6 and miR-21, which can be attenuated by CDF treatment. PLoS One 7(12):e50165. doi:10.1371/journal.pone.0050165

Bao B, Ali S, Banerjee S, Wang Z, Logna F, Azmi AS et al (2012d) Curcumin analogue CDF inhibits pancreatic tumor growth by switching on suppressor microRNAs and attenuating EZH2 expression. Cancer Res 72(1):335–345. doi:10.1158/0008-5472.CAN-11-2182

Ben-Neriah Y, Karin M (2011) Inflammation meets cancer, with NF-kappaB as the matchmaker. Nat Immunol 12(8):715–723. doi:10.1038/ni.2060

Chan B, Manley J, Lee J, Singh SR (2015) The emerging roles of microRNAs in cancer metabolism. Cancer Lett 356(2 Pt A):301–308. doi:10.1016/j.canlet.2014.10.011

Dandawate PR, Vyas A, Ahmad A, Banerjee S, Deshpande J, Swamy KV et al (2012) Inclusion complex of novel curcumin analogue CDF and beta-cyclodextrin (1:2) and its enhanced in vivo anticancer activity against pancreatic cancer. Pharm Res 29(7):1775–1786. doi:10.1007/s11095-012-0700-1

Fu X, Han Y, Wu Y, Zhu X, Lu X, Mao F et al (2011) Prognostic role of microRNA-21 in various carcinomas: a systematic review and meta-analysis. Eur J Clin Invest 41(11):1245–1253. doi:10.1111/j.1365-2362.2011.02535.x

Gao W, Xu J, Liu L, Shen H, Zeng H, Shu Y (2012) A systematic-analysis of predicted miR-21 targets identifies a signature for lung cancer. Biomed Pharmacother 66(1):21–28. doi:10.1016/j.biopha.2011.09.004

Gul K, Singh AK, Jabeen R (2015) Nutraceuticals and functional foods: the foods for future world. Crit Rev Food Sci Nutr. doi:10.1080/10408398.2014.903384

Gupta SC, Kismali G, Aggarwal BB (2013a) Curcumin, a component of turmeric: from farm to pharmacy. Biofactors 39(1):2–13. doi:10.1002/biof.1079

Gupta SC, Patchva S, Aggarwal BB (2013b) Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J 15(1):195–218. doi:10.1208/s12248-012-9432-8

Hata A, Lieberman J (2015) Dysregulation of microRNA biogenesis and gene silencing in cancer. Sci Signal 8(368):re3. doi:10.1126/scisignal.2005825

Howells LM, Mahale J, Sale S, McVeigh L, Steward WP, Thomas A et al (2014) Translating curcumin to the clinic for lung cancer prevention: evaluation of the preclinical evidence for its utility in primary, secondary, and tertiary prevention strategies. J Pharmacol Exp Ther 350(3):483–494. doi:10.1124/jpet.114.216333

Kanwar SS, Yu Y, Nautiyal J, Patel BB, Padhye S, Sarkar FH et al (2011) Difluorinated-curcumin (CDF): a novel curcumin analog is a potent inhibitor of colon cancer stem-like cells. Pharm Res 28(4):827–838. doi:10.1007/s11095-010-0336-y

Li Y, Kong D, Wang Z, Ahmad A, Bao B, Padhye S et al (2011) Inactivation of AR/TMPRSS2-ERG/Wnt signaling networks attenuates the aggressive behavior of prostate cancer cells. Cancer Prev Res 4(9):1495–1506. doi:10.1158/1940-6207.CAPR-11-0077

Liu J, Zhu H, Yang X, Ge Y, Zhang C, Qin Q et al (2014) MicroRNA-21 is a novel promising target in cancer radiation therapy. Tumour Biol 35(5):3975–3979. doi:10.1007/s13277-014-1623-8

Padhye S, Yang H, Jamadar A, Cui QC, Chavan D, Dominiak K et al (2009a) New difluoro Knoevenagel condensates of curcumin, their Schiff bases and copper complexes as proteasome

inhibitors and apoptosis inducers in cancer cells. Pharm Res 26(8):1874–1880. doi:10.1007/s11095-009-9900-8

Padhye S, Banerjee S, Chavan D, Pandye S, Swamy KV, Ali S et al (2009b) Fluorocurcumins as cyclooxygenase-2 inhibitor: molecular docking, pharmacokinetics and tissue distribution in mice. Pharm Res 26(11):2438–2445. doi:10.1007/s11095-009-9955-6

Padhye S, Chavan D, Pandey S, Deshpande J, Swamy KV, Sarkar FH (2010) Perspectives on chemopreventive and therapeutic potential of curcumin analogs in medicinal chemistry. Mini Rev Med Chem 10(5):372–387

Pan X, Wang ZX, Wang R (2010) MicroRNA-21: a novel therapeutic target in human cancer. Cancer Biol Ther 10(12):1224–1232

Rahmani AH, Al Zohairy MA, Aly SM, Khan MA (2014) Curcumin: a potential candidate in prevention of cancer via modulation of molecular pathways. Biomed Res Int 2014:761608. doi:10.1155/2014/761608

Roy S, Yu Y, Padhye SB, Sarkar FH, Majumdar AP (2013) Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21. PLoS One 8(7):e68543. doi:10.1371/journal.pone.0068543

Sarkar FH, Li Y (2008) NF-kappaB: a potential target for cancer chemoprevention and therapy. Front Biosci 13:2950–2959

Sarkar FH, Li Y, Wang Z, Kong D (2008) NF-kappaB signaling pathway and its therapeutic implications in human diseases. Int Rev Immunol 27(5):293–319. doi:10.1080/08830180802276179

Sarkar FH, Li Y, Wang Z, Padhye S (2010) Lesson learned from nature for the development of novel anti-cancer agents: implication of isoflavone, curcumin, and their synthetic analogs. Curr Pharm Des 16(16):1801–1812

Sethi S, Li Y, Sarkar FH (2013) Regulating miRNA by natural agents as a new strategy for cancer treatment. Curr Drug Targets 14(10):1167–1174

Sethi S, Ali S, Sethi S, Sarkar FH (2014) MicroRNAs in personalized cancer therapy. Clin Genet 86(1):68–73. doi:10.1111/cge.12362

Shanmugam MK, Rane G, Kanchi MM, Arfuso F, Chinnathambi A, Zayed ME et al (2015) The multifaceted role of curcumin in cancer prevention and treatment. Molecules 20(2):$32#2728–2769. doi:10.3390/molecules20022728

Sheedy FJ (2015) Turning 21: Induction of miR-21 as a Key Switch in the Inflammatory Response. Front Immunol 6:19. doi:10.3389/fimmu.2015.00019

Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65(1):5–29. doi:10.3322/caac.21254

Syed DN, Suh Y, Afaq F, Mukhtar H (2008) Dietary agents for chemoprevention of prostate cancer. Cancer Lett 265(2):167–176. doi:10.1016/j.canlet.2008.02.050

Tkach KE, Oyler JE, Altan-Bonnet G (2014) Cracking the NF-kappaB code. Sci Signal 7(313):e5. doi:10.1126/scisignal.2005108

Vallianou NG, Evangelopoulos A, Schizas N, Kazazis C (2015) Potential anticancer properties and mechanisms of action of curcumin. Anticancer Res 35(2):645–651

Vidigal JA, Ventura A (2015) The biological functions of miRNAs: lessons from in vivo studies. Trends Cell Biol 25(3):137–147. doi:10.1016/j.tcb.2014.11.004

Wu L, Zhao JC, Kim J, Jin HJ, Wang CY, Yu J (2013) ERG is a critical regulator of Wnt/LEF1 signaling in prostate cancer. Cancer Res 73(19):6068–6079. doi:10.1158/0008-5472.CAN-13-0882

Xue J, Niu J, Wu J, Wu ZH (2014) MicroRNAs in cancer therapeutic response: friend and foe. World J Clin Oncol 5(4):730–743. doi:10.5306/wjco.v5.i4.730

Prostate Cancer Chemoprevention by Dietary Agents: Advocating a Personalized Multi-agent Approach

Vaqar Mustafa Adhami and Hasan Mukhtar

Abstract Cancer chemoprevention research is rapidly evolving and our knowledge about the disease constantly updated. There is increasing acceptance of the fact that cancer is as diverse as the individual is and therefore needs a personalized rather than a generalized approach. This is true for chemoprevention but is also valid for chemotherapeutic intervention. Chemoprevention refers to the use of agents to intervene in the process of carcinogenesis with the intention to delay or inhibit the progression of cancer. Of all cancers, prostate cancer (PCa) is considered an ideal disease for chemopreventive intervention because its long latency provides a substantial opportunity to delay the onset of clinically detectable disease. Chemopreventive interventions need to be widely accepted and nontoxic since they would run over long periods of time and in usually healthy populations. In search for safe and nontoxic chemopreventive agents, many naturally occurring bioactive food components, capable of affording protection against carcinogenesis, have been defined. While laboratory studies with these agents have been promising, clinical trials have not yielded desired results. Considering the fact that carcinogenesis is a multistep process, it is unlikely that single-agent approach could prove effective in preventing cancer in individuals. We support the need to build an armamentarium of mechanism-based naturally occurring chemopreventive substances that could prevent or slow down the development and progression of cancer in general and use their tailored combination in different populations based on identified risk factors. Thus, the new effective approach for cancer chemoprevention prevention "building a customized mechanism-based chemoprevention cocktail of naturally occurring substances" is advocated.

V.M. Adhami • H. Mukhtar (✉)
University of Wisconsin, School of Medicine and Public Health, Medical Sciences Center-4385, 1300 University Avenue, Madison, WI 53706, USA
e-mail: hmukhtar@wisc.edu

M.F. Ullah, A. Ahmad (eds.), *Critical Dietary Factors in Cancer Chemoprevention*,
DOI 10.1007/978-3-319-21461-0_2

1 Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related deaths among males in the United States (Siegel et al. 2015). According to estimates of the American Cancer Society, in the year 2015, approximately 220,800 new cases of PCa and 27,540 PCa-related deaths are predicted (Siegel et al. 2015). From a practical point of view, the most effective means of controlling PCa or the morbidity associated with its treatment is to establish effective chemopreventive approaches to block, reverse, or delay the process of carcinogenesis (Mukhtar 2012; Adhami and Mukhtar 2013). Whereas the diagnosis and treatment of patients with early-stage disease have markedly improved, the prognosis of patients with advanced stages of disease is still very poor. The concept of reduction of PCa occurrence by means of dietary intervention is gaining popularity and wide acceptance as PCa patients are increasingly using botanical supplements (Adhami and Mukhtar 2013). For a variety of reasons, the most important of which is human acceptance, dietary substances for chemoprevention are preferred (Adhami and Mukhtar 2013).

It is important to note that studies around the world have indicated a positive association of dietary agents in prevention and possibly cure of PCa. In recent years, much progress has been made in this direction, which has led to the identification of novel PCa chemopreventive agents (Lall et al. 2015). However, the prevailing approach for cancer chemoprevention has been "Find effective agents, with none to acceptable adverse effects and use them in relatively healthy individuals or in people stated for high risk for cancer development." This wisdom has not yielded desired results because clinical trials of single agents have ended with disappointing results. We argue that the lesson from these trials is that "One-size-fits-all approach is inappropriate." This is understandable since the process of carcinogenesis is multistep and multifactorial.

We advocate a three-step new approach for cancer chemoprevention under which there is a need to (1) establish the signature of defects in the individuals for whom chemoprevention is sought, (2) build an armamentarium of chemopreventive substances that could ameliorate defined biochemical defect(s) that occur in the carcinogenesis process, and (3) develop a customized cocktail, preferably dietary in nature, that the individual could be persuaded to consume (Fig. 1). At first thought this goal appears simple; however, it also raises many issues related to effectiveness and toxicity of each selected agent in a cocktail. However, in years to come, these issues could be resolved.

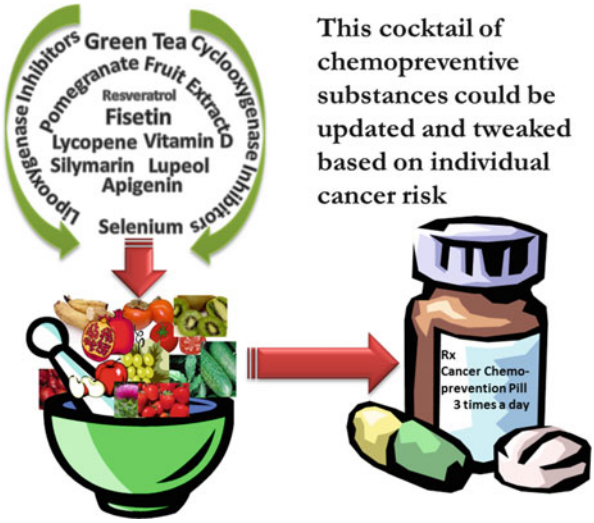

Fig. 1 Developing a prostate cancer chemoprevention cocktail. Cancer is as diverse as the individual is and therefore needs a personalized rather than a generalized approach. Also, carcinogenesis is a multistep process; it is unlikely that single-agent approach could prove effective in preventing cancer. In search for safe and nontoxic chemopreventive agents, many naturally occurring bioactive food components, capable of affording protection against carcinogenesis, have been defined. Thus, the new effective approach for cancer prevention "building a customized mechanism-based chemoprevention cocktail of naturally occurring substances" is advocated

2 Diet in Causation and Prevention of Cancer

Diet is a complex mixture of chemicals and thus for cancer risk is a mixed bag of bad and good stuff, carcinogens and anticarcinogens, respectively. Current evidence for the involvement of diet in cancer etiology is based on convincing laboratory data where dietary manipulations in rodent tumor bioassay protocols have established a definite link. Much of the knowledge of the role of diet in human cancer outcome however is based on indirect relationships between the consumption of selected food constituents and dietary habits and incidence of cancer at various sites. The indirect evidence, most often referred to, is the suggested correlation between the complex of fats-meat-egg-animal protein and the risk for cancer of various organs (Modan 1977). Carcinogenic agents identified include food additives, plant toxicants, aflatoxins, polycyclic hydrocarbons, nitrosamines, and certain normal major food constituents (Modan 1977). A synergistic action of ingested or metabolized carcinogens and a co-carcinogenic function of certain dietary components are suggested. Abundant epidemiological, observational, and metabolic biomarker studies have provided convincing evidence that nutrition plays an important causative role in the initiation, promotion, and progression stages of several types of human cancers [(Mukhtar and Ahmad 1999) and the