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THE MOLECULAR TARGETS AND THERAPEUTIC USES OF CURCUMIN IN HEALTH AND DISEASE
Edited by Bharat B. Aggarwal, Young-Joon Surh and Shishir Shishodia

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Bharat B. Aggarwal
Young-Joon Surh
Shishir Shishodia
Editors

The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease

With 77 Illustrations

Springer

Editors

Bharat B. Aggarwal, Ph.D.
Ransom Horne, Jr., Professor of Cancer Research
Professor of Cancer Medicine (Biochemistry)
and Chief, Cytokine Research Section
Department of Experimental Therapeutics
The University of Texas M. D. Anderson Cancer Center
1515 Holcombe Boulevard, BOX 143, Houston, TX 77030, USA
aggarwal@mdanderson.org

Young-Joon Surh, Ph.D.
Chief and Professor
National Research Laboratory of Molecular Carcinogenesis
and Chemoprevention
College of Pharmacy
Seoul National University
Shillim-dong, Kwanak-gu, Seoul 151-742, South Korea
surh@plaza.snu.ac.kr

Shishir Shishodia, Ph.D.
Assistant Professor
Department of Biology
Texas Southern University
3100 Cleburne Street, Houston, TX 77004, USA
shishodia@gmail.com

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Dedicated to our gurus and parents whose guidance continues to inspire us!

Sarve bhavantu sukhinah sarve santu niramayah
Sarve bhadrani pasyantu ma kascid duhkhabhag bhavet

"May all be happy; may all be healthy;
may all enjoy prosperity; may none suffer."

PREFACE

The subject of this monograph, curcumin, which gives the yellow color to turmeric, best known as *Haridra* in Sanskrit (means dear to Hari or Lord Krishna). Turmeric is known by several synonyms related to its appearance or use, including *Pita* (yellow, leading to the name *Peethamber dhari* for Lord Krishna based on wearing only yellow clothes), *Gauri* (brilliant), *Kanchani* (looks like gold), *Nisha* (beautiful as a full moon night), *Krimighni* (antibacterial and antihelmenthic), *Mahaghni* (antidiabetic), and *Yoshit priya* (gynecological disorders). In Hindi, turmeric is known as *Haldi*, in Japanese as *Ukon* or *Gajyutsu*, and in Korean as *Ulgeum* or *Gangwhang*.

Turmeric is mentioned in the writings of the Italian explorer Marco Polo, who was introduced to it during his voyage to China and India around 1290 AD. Although he gets credit for bringing Far East spices to Europe, turmeric was actually introduced in Europe in the 13th century AD by Arab traders. The Portuguese explorer Vasco de Gama visited the Indian subcontinent during the 15th century and brought turmeric and other spices of the Orient to the West. It was only during the rule of the British in India that turmeric was combined with various other spices and renamed "curry powder," as it is called in the West.

Turmeric became of special importance to man with the discovery that when added to various food preparations, its dried and powdered rhizome preserved their freshness and nutritive value and improved the palatability and presentation of food. The brilliant yellow color of turmeric, which persists even at very high dilutions, found its way to commercial use as a coloring agent for various items, including cotton, silk, paper, wood, foodstuffs, and cosmetics. In Ayurveda (science of long life), turmeric has been used internally as a stomachic, tonic, and blood purifier and topically in the prevention and treatment of skin diseases. Turmeric concoctions have been traditionally used for the treatment of flatulence, dyspepsia, liver disorder, jaundice, urinary tract diseases, cold, chronic otorrhea, parasitic skin infection, bruises, sprain, wound, infected wound, and inflammation.

We are currently living in an era when 80% of the world's population cannot afford modern medicine. Even for those 20% who can, much of modern medicine is ineffective and has numerous side effects. It is a good time to revive the medicinal use of the ancient medicine curcumin. In this volume we bring together the contribution of modern science to one of the most ancient spices known to mankind. Curcumin's beneficial role in health and disease and its molecular targets are the focus of this monograph. This volume is directed at clinicians and scientists working in the areas of experimental and molecular therapeutics, molecular medicine, translational cancer research, Ayurveda, herbal medicine, naturopathy, and biomedical sciences in general and, most importantly, to the end users of curcumin. We hope that this book will "add spice to everybody's life."

We would like to thank all of the contributors for their valuable contributions to this work. We would also like to thank those who have contributed significantly to curcumin research but could not, because of limitations on space, be invited to contribute.

Bharat B. Aggarwal, Ph.D.
Young-Joon Surh, Ph.D.
Shishir Shishodia, Ph.D.

FOREWORD

It is indeed a matter of pride and privilege to write the Foreword; to this scholarly contribution on curcumin—the major constituent of turmeric. The volume has been successful in seamlessly connecting the traditional knowledge available on turmeric to the findings of systematic modern research on turmeric and, based on this effort, building the possibilities of developing novel drugs to treat diverse diseases. Turmeric (*Curcuma longa*)—a widely cultivated tropical plant—has been used since ancient times as a spice, as a beauty care agent, and as a traditional medicine.

The rhizome of turmeric is highly aromatic and antiseptic. The medicinal properties of turmeric have been expounded in Ayurvedic and traditional Chinese medicine (TCM) texts. Turmeric is traditionally known as a stomachic, blood purifier and is useful for the common cold, leprosy, intermittent fevers, afflictions of the liver, indolent ulcer, pyogenic (forming pus) afflictions, wound-healing, and inflammation.

In recent years, the medicinal properties of turmeric have increasingly been recognized. It is being researched systematically even in the Western world. I remember fighting the "turmeric battle" on the wrong patent on the wound-healing properties of turmeric that was given by the US Patent Office almost a decade ago.

As per the US National Library of Medicine, 256 research papers were published last year on curcumin. The researchers have found in curcumin a near-perfect starting material for drug discovery. Thus, a variety of curcumin analogues have been prepared and evaluated biologically. Curcumin exhibits a wide range of activities [e.g., antibacterial, anti-inflammatory, hypolipidemic, hepatoprotective, lipoxygenase (LOX), cyclooxygenase (COX), protease inhibitory effects, in addition to being effective as an active oxygen scavenger and lipid peroxidase (a class of oxidoreductase enzymes) inhibitor]. Curcumin and the curcuminoids also lower cholesterol, reduce platelet aggregation, inhibit the proliferation of cancer cells, and improve digestion by increasing the flow of bile from the gallbladder. The desirable preventive or putative therapeutic properties of curcumin have been considered to be associated with its antioxidant and anti-inflammatory properties.

Curcumin has been found to modulate the activity of several key transcription factors and, in turn, the cellular expression profiles. The effect of curcumin has been examined on most of the targets discovered within the last three decades. Curcumin modulates several different transcription factors, cytokines, growth factors, kinases and other enzymes. The research results have been elaborately covered in this book and explanations provided would add to knowledge pool.

The National Institutes of Health has four clinical trials in progress on curcumin treatment, namely for pancreatic cancer, multiple myeloma, Alzheimer's disease, and colorectal cancer. Curcumin has been found to possess potential

chemopreventive activities. It shows cytotoxic potential against tumor cells both *in vitro* and *in vivo*. Thus, curcumin fits well in the effort of chemoprevention by edible phytochemicals, which is now considered to be an inexpensive, readily applicable, and accessible approach to cancer management. The optimization of intervention trials of diet-derived putative chemopreventive agents is currently under development in normal populations as well as in high- risk groups. Curcumin is also a good immunomodulator. These biological activities warrant further studies of curcumin in the treatment and prevention of human neoplasm.

Curcumin has enormous potential as an antiangiogenic drug. It has been elaborately explained in the chapter discussing this. The property has been attributed to curcumin's ability to downregulate certain transcription factors and proangiogenic factors. Curcumin also has the necessary characteristics of a neuroprotective drug. The activity has been proven in a variety of disease models. Thus, it has great potential for the prevention of multiple neurological conditions for which current therapeutics are less than optimal. The chapter entitled "Neuroprotective Effects of Curcumin" embodies the research carried out on the subject and the existing necessity for further efforts. The curcumin-mediated regulation of COX and LOX enzymes for obtaining their beneficial effects in preventing diverse inflammatory diseases has been dwelt upon in another chapter. Interestingly, curcumin has an edge over conventional nonsteroidal anti-inflammatory drugs and selective COX-2 inhibitors. This might pave the way for path-breaking research in the domain.

This volume in fact covers the length and breadth of research undertaken on curcumin and research results thus far obtained. The diversity ranges from molecular targets, cell growth regulation, antioxidant and anti-inflammatory properties, chemosensitivity, radio protection, and radio sensitivity to immunomodulation, anticancer effects, cardioprotective effects, nephroprotective to hepatoprotective effects, protection from acute and chronic lung diseases to pharmacokinetics and pharmacodynamics and clinical studies undertaken with curcumin. The canvas thus covered is indeed brilliant.

As research advances, it poses newer challenges as well. Several questions in the light of the new drug development effort thus remain to be answered in order to put curcumin in a higher orbit. These pertain to the solubility and stability of curcumin, its optimum dose, pharmacokinetics, mechanism of action of curcumin for a given disease, bioavailability profile, and intricacies of prevention and cure of an identified disease. Further research is thus necessary on these aspects. There is also a need to find out whether other components of turmeric than curcumin have beneficial effects, either alone or in combination with curcumin.

I am happy to see that the contributions in this book have proven beyond doubt that curcumin—an ingredient of the traditional Indian spice turmeric—has enormous potential against a variety of malignant and nonmalignant diseases. I am confident that the state-of-the-art on curcumin research so nicely compiled and analyzed throughout this volume would provide an insight and learning not only to professionals in the field but also to budding researchers. I hope that they would be inspired to answer the unanswered questions on curcumin based on new research

endeavors. I congratulate the editors of the volume and the contributors of the various chapters for creating this unique and scholarly marvel.

R.A. Mashelkar, FRS
Director General
Council of Scientific & Industrial Research, New Delhi, India
October 19, 2006

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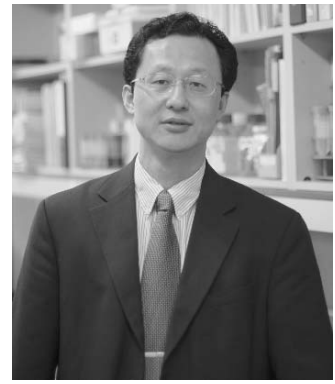
EDITORS

Dr. Bharat B. Aggarwal received his Ph.D. in Biochemistry from the University of California, Berkeley, did his postdoctoral fellowship in endocrinology at the University of California Medical Center San Francisco, and then worked for a biotechnology company (Genentech Inc.) where he discovered two different TNFs, both essential components of the immune system. In 1989, Dr. Aggarwal accepted a position as a Professor and Chief of the Cytokine Research Section at the University of Texas M. D. Anderson Cancer in Houston. He currently holds the Ransom Horne Jr. Professorship in Cancer Research. He has published over 400 original peer-reviewed articles and reviews, edited 9 books, and been granted almost 35 patents. Since 2001, Dr. Aggarwal has been listed as one of the world's most highly cited scientists by the Institute of Scientific Information. Dr. Aggarwal received an Outstanding Scientists Award from Ranbaxy in 2005 and from the American Association of Indians in Cancer Research in 2006.

Dr. Young-Joon Surh is a Professor of Biochemistry and Molecular Toxicology, College of Pharmacy, Seoul National University, South Korea and Chief of National Research Laboratory of Molecular Carcinogenesis and Chemoprevention. Professor Surh earned a Ph.D. degree at the McArdle Laboratory for Cancer Research, University of Wisconsin–Madison and completed postdoctoral training at the Massachusetts Institute of Technology. In 1992, he was appointed as a tenure-track assistant professor at Yale University School of Medicine. Since relocating to Seoul National University in 1996, he has been leading the Chemoprevention Working Group, investigating the molecular mechanisms of cancer prevention by edible phytochemicals, with emphasis on intracellular signaling molecules as prime targets. He is currently a member of the editorial boards of more than 10 international journals, including *Carcinogenesis, Molecular Carcinogenesis, Cancer Letters, Mutation Research, Food and Chemical Toxicology, and Biofactors.* He is also



co-editor of the book *Oxidative Stress, Inflammation and Health* published by CRC Press in 2005. Dr. Surh has published more than 120 papers in peer-reviewed international journals and about 50 invited editorials, reviews, and book chapters. Dr. Surh has recently published a seminal article, entitled "Chemoprevention with Dietary Phytochemicals," in *Nature Reviews Cancer*.

Dr. Shishir Shishodia earned his Ph.D. in Biotechnology from Banaras Hindu University, Varanasi, India and did his postdoctoral fellowship at the University of Texas M. D. Anderson Cancer Center. Before joining M. D. Anderson Cancer Center, he served as an Assistant Professor at Patna University, Patna, India. He is currently an Assistant Professor at the Texas Southern University, Houston. Dr. Shishodia's research interests include cytokine signaling, the role of transcription factors in tumorigenesis, and regulation of transcription by natural products. He has identified several natural compounds that exhibit anticancer properties. He has published over 50 peer-reviewed papers and co-edited the book *Resveratrol in Health and Disease*. Dr. Shishodia is a recipient of the BHU Gold Medal and the Theodore N. Law Odyssey Award for outstanding scientific achievements.

CONTRIBUTORS

Bharat B. Aggarwal
Ransom Horne, Jr., Professor of Cancer Research
Professor of Cancer Medicine (Biochemistry) and
Chief, Cytokine Research Section
Department of Experimental Therapeutics
The University of Texas M.D. Anderson Cancer Center
1515 Holcombe Boulevard
BOX 143
Houston, TX 77030, USA
aggarwal@mdanderson.org

Jack L. Arbiser
Associate Professor
Department of Dermatology, Emory University School of Medicine
Winship Cancer Institute
1639 Pierce Drive WMB 5309
Atlanta, GA 30322, USA
jarbise@emory.edu

Mary Babu
Deputy Director and Head
Bio-Materials Laboratory
CLRI, Chennai-600020, India
marybabu@hotmail.com

Sulochana S. Bhandarkar
Department of Dermatology
Emory University School of Medicine
Winship Cancer Institute
1639 Pierce Drive WMB 5309
Atlanta, GA 30322, USA
ssbhand@emory.edu

John J. Bright
Senior Investigator and Director of Neuroscience Research Laboratory
Methodist Research Institute
Clarian Health, 1800 N Capital Avenue
Noyes Building, Suite E504
Indianapolis, IN 46202, USA
jbright1@clarian.org

Madan M. Chaturvedi
Professor
Department of Zoology
Delhi University
Delhi 110007, India
mchaturvedi@zoology.du.ac.in

Ann-Lii Cheng
Professor
Department of Internal Medicine and Oncology, National Taiwan University Hospital
Cancer Research Center, National Taiwan University College of Medicine
7 Chung-Shan S. Rd., Taipei, Taiwan
andrew@ha.mc.ntu.edu.tw

Kyung-Soo Chun
Laboratory of Molecular Carcinogenesis
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709, USA
chunkyungsoo@yahoo.co.kr

Gregory M. Cole
Professor of Medicine and Neurology
Greater Los Angeles Veterans Affairs Healthcare System

Geriatric Research, Education, and
Clinic Center 11E
16111 Plummer Street
Sepulveda, CA 91343, USA
gmcole@ucla.edu

Scott Dulchavsky
Department of Surgery
Henry Ford Health System
2977 West Grand Boulevard
Detroit, MI 48202, USA
sdulcha1@hfhs.org

Sally A. Frautschy
Associate Professor of Neurology
Department of Medicine and
Neurology
University of California,
Los Angeles
Greater Los Angeles Healthcare
System
(Veteran's Affairs Medical Center)
16111 Plummer St. North Hills,
CA 91343, USA
frautsch@ucl.edu

Xiaohua Gao
Department of Surgery
Henry Ford Health System
2977 West Grand Boulevard
Detroit, MI 48202, USA
tgao1@hfhs.org

Subhash C. Gautam
Department of Surgery
Henry Ford Health System
2977 West Grand Boulevard
Detroit, MI 48202, USA
sgautam1@hfhs.org

Andreas J. Gescher
Professor of Biochemical Toxicology
Cancer Biomarkers and Prevention
Group
Department of Cancer Studies and
Molecular Medicine
University of Leicester
Leicester LE2 7LX, UK
ag15@leicester.ac.uk.

Chandrasekharan Guruvayoorappan
Department of Immunology
Amala Cancer Research Centre
Amala Nagar, Thrissur Kerala 680555,
India
guru_appa2003@yahoo.co.in

Chih-Hung Hsu
Department of Oncology
National Taiwan University Hospital
7, Chung-Shan S. Rd., Taipei, Taiwan
chih@ha.mc.ntu.edu.tw

Haruyo Ichikawa
International Research and Educational
Institute for Integrated Medical
Sciences
Tokyo Women's Medical School
8-1 Kawada-cho, Shinjuku
Tokyo 162-8666, Japan
haruyo.ichikawa@gmail.com

Ganesh C. Jagetia
Professor & Head
Department of Radiobiology
Kasturba Medical College
Manipal—576 104, India
gc.jagetia@gmail.com

Jeena Joseph
Department of Cancer Biology
Rajiv Gandhi Centre for
Biotechnology
Thiruvananthapuram-695 014, India
josephjeena@gmail.com

Devarajan Karunagaran
Professor
Department of Biotechnology

Indian Institute of Technology Madras
Chennai - 600 036, India
karuna@iitm.ac.in

Kuzhuvelil B. Hari Kumar
Department of Biochemistry
Amala Cancer Research Centre
Amala Nagar, Thrissur Kerala, India
kbharikumar@gmail.com

Thankayyan R. Santhosh Kumar
Department of Cancer Biology
Rajiv Gandhi Centre for Biotechnology
Thiruvananthapuram-695 014, India
santhaltr@yahoo.com

Girija Kuttan
Professor
Department of Immunology
Amala Cancer Research Centre
Amala Nagar, Thrissur Kerala, India
amalaresearch@rediffmail.com

Ramadasan Kuttan
Research Director
Amala Cancer Research Centre
Amala Nagar, Thrissur
Kerala, India
amalaresearch@rediffmail.com

Pornngarm Limtrakul
Chairperson, Department of
Biochemistry
Faculty of Medicine
Chiang Mai University
Chiang Mai, Thailand 50200
plimtrak@mail.med.cmu.ac.th

Jen-Kun Lin
Professor
Institute of Biochemistry and
Molecular Biology
College of Medicine
National Taiwan University
No. 1, Section 1, Jen-ai Road
Taipei, Taiwan
jklin@ha.mc.ntu.edu.tw

Dennis C. Liotta
Professor of Organic Chemistry
Department of Chemistry
Emory University
Atlanta, GA, 30322, USA
dliotta@emory.com

Radha K. Maheshwari
Professor of Pathology
Director, Center for Combat Casualty
and Life Sustainment Research
Coordinator Indo-US activities
Uniformed Services University of the
Health Sciences
Bethesda, MD 20814, USA
rmaheshwari@usuhs.mil

Nikita Malani
Cytokine Research Laboratory
Department of Experimental
Therapeutics - Box 143
University of Texas M. D. Anderson
Cancer Center
1515 Holcombe Boulevard
Houston, Texas, USA
nmalani@sas.upenn.edu

Venugopal P. Menon
Professor and Chairman
Department of Biochemistry &
Center for Micronutrient Research
Annamalai University
Annamalai Nagar-608 002
Chidambaram, Tamilnadu, India
biocmr@sify.com

Sumitra Miriyala
Department of Medicine
Carolina Cardiovascular Biology
Center
University of North Carolina

Chapel Hill, North Carolina-27599, USA
sumishree@hotmail.com

Cara A. Mosley
Department of Chemistry
Emory University
Atlanta, GA, 30322, USA
camosle@emory.edu

Toshihiko Osawa
Professor
Laboratory of Food and Biodynamics
Nagoya University Graduate School of Bioagricultural Sciences
Furo-cho, Chikusa-ku, Nagoya
464-8601, Japan
osawat@agr.nagoya-u.ac.jp

Manikandan Panchatcharam
Department of Medicine
Carolina Cardiovascular Biology Center
University of North Carolina
Chapel Hill, North Carolina 27599, USA
spmani5@gmail.com

Durairaj Punithavathi
Bio-materials Laboratory
CLRI, Adyar, Chennai-600020, India
punithavathid@yahoo.com

Chinthalapally V. Rao
Professor of Medicine
Kerley-Cade Endowed Chair in Cancer Research
Hematology-Oncology Section
Director, Chemoprevention Program
University of Oklahoma Cancer Institute
OUHSC, P.O. Box 26901
975 NE 10th Street, BRC 1203
Oklahoma City, OK 73104, USA
cv-rao@ouhsc.edu

Puvanakrishnan Rengarajulu
Deputy Director and Head
Department of Biotechnology
CLRI, Chennai-600 020
India
puvanakrishnan@yahoo.com

Adluri Ram Sudheer
Department of Biochemistry & Biotechnology
Faculty of Science
Annamalai University
Annamalai Nagar-608002, Tamilnadu, India
biosudheer99@yahoo.co.in

Anuj Sharma
Uniformed Services University of Health Sciences,
Bethesda, MD, USA
Birla Institute of Technology and Science
Pilani 333031, Rajasthan, India
asharma@usuhs.mil

Ricky A. Sharma
Senior Fellow & Honorary Consultant Radiation Oncology & Biology,
University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK
ricky.sharma@rob.ox.ac.uk

Shishir Shishodia
Assistant Professor
Department of Biology
Texas Southern University
3100 Cleburne Street
Houston, TX 77004, USA
shishodia@gmail.com;
shishodias@tsu.edu

Tulika Singh
Department of Biology
Texas Southern University

3100 Cleburne Street
Houston, TX 77004, USA
tsshishodia@gmail.com

James P. Snyder
Director of Biostructural Research
Department of Chemistry
Emory University
1515 Dickey Drive
Atlanta, GA 30322, USA
jsnyder@emory.edu

William P. Steward
Professor of Oncology
Cancer Biomarkers and Prevention Group
Department of Cancer Studies and Molecular Medicine
University of Leicester
Leicester Royal Infirmary
Leicester LE1 SWW, UK
wps1@leicester.ac.uk

Chitra Sundaram
Cytokine Research Laboratory
Department of Experimental Therapeutics - Box 143
University of Texas M. D. Anderson Cancer Center
1515 Holcombe Boulevard
Houston, Texas, USA
chitra_1964@yahoo.com

Young-Joon Surh
Chief and Professor
National Research Laboratory of Molecular Carcinogenesis and Chemoprevention
College of Pharmacy
Seoul National University
Shillim-dong, Kwanak-gu
Seoul 151-742, South Korea
surh@plaza.snu.ac.kr

Bruce Teter
Department of Medicine and Neurology
University of California, Los Angeles
Greater Los Angeles Healthcare System
(Veteran's Affairs Medical Center)
16111 Plummer St. North Hills, CA 91343, USA
bteter@ucla.edu

Rajesh L. Thangapazham
Uniformed Services University of Health Sciences
Bethesda, MD, USA
Birla Institute of Technology and Science
Pilani 333031, Rajasthan, India
rlthangapazham@usuhs.mil

Narayanan Venkatesan
Associate Professor
Faculte de Medecine
UMR-7561 CNRS UHP; B.P. 184
54505 Vandoeuvre lès Nancy
France
vnar12@yahoo.com

CURCUMIN: THE INDIAN SOLID GOLD

Bharat B. Aggarwal, Chitra Sundaram, Nikita Malani,
and Haruyo Ichikawa

Abstract: Turmeric, derived from the plant *Curcuma longa*, is a gold-colored spice commonly used in the Indian subcontinent, not only for health care but also for the preservation of food and as a yellow dye for textiles. Curcumin, which gives the yellow color to turmeric, was first isolated almost two centuries ago, and its structure as diferuloylmethane was determined in 1910. Since the time of Ayurveda (1900 BC) numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, including those of the skin, pulmonary, and gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. Extensive research within the last half century has proven that most of these activities, once associated with turmeric, are due to curcumin. Curcumin has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease, and other chronic illnesses. These effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. Curcumin exhibits activities similar to recently discovered tumor necrosis factor blockers (e.g., HUMIRA, REMICADE, and ENBREL), a vascular endothelial cell growth factor blocker (e.g., AVASTIN), human epidermal growth factor receptor blockers (e.g., ERBITUX, ERLOTINIB, and GEFTINIB), and a HER2 blocker (e.g., HERCEPTIN). Considering the recent scientific bandwagon that multitargeted therapy is better than monotargeted therapy for most diseases, curcumin can be considered an ideal *"Spice for Life"*.

1. INTRODUCTION

The questions of whether medicines discovered today are safer, more efficacious, and more affordable than generic medicines (whose patents have expired) or medicines that are centuries old could be answered "no" for most of the modern medicines. If so, then it is logical to revisit and revive these age-old medicines for the welfare of mankind. Curcumin is one such medicine. Its history goes back over 5000 years, to the heyday of Ayurveda (which means the science of long life). Turmeric derived from the rhizome of the plant *Curcuma longa* has

been used by the people of the Indian subcontinent for centuries with no known side effects, not only as a component of food but also to treat a wide variety of ailments.

Turmeric is a spice of golden color that is used in cooking in the Indian subcontinent. Because of its color and taste, turmeric was named "Indian saffron" in Europe. Today, India is the primary exporter of turmeric (known as haldi in India). Although its ability to preserve food through its antioxidant mechanism, to give color to food, and to add taste to the food is well known, its health-promoting effects are less well recognized or appreciated. It was once considered a cure for jaundice, an appetite suppressant, and a digestive. In Indian and Chinese medicines, turmeric was used as an anti-inflammatory agents to treat gas, colic, toothaches, chest pains, and menstrual difficulties. This spice was also used to help with stomach and liver problems, to heal wounds and lighten scars, and as a cosmetic.

Turmeric was mentioned in the writings of Marco Polo concerning his 1280 journey to China and India and it was first introduced to Europe in the 13th century by Arab traders. Although Vasco de Gama (a Portugeese sailor) during 15th century, after his visit to India, truly introduced spices to the West, it was during the rule of British in India that turmeric was combined with various other spices and renamed "curry powder," as it is called in the West. What is there in turmeric that has therapeutic potential, how does this substance mediates its effects, with what types of receptor does it interact, and for what type of diseases is it effective? All of these questions will be addressed in this review.

2. COMPOSITION OF TURMERIC

Turmeric contains a wide variety of phytochemicals, including curcumin, demethoxycurcumin, bisdemethoxycurcumin, zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols.[1] Curcumin, demethoxycurcumin, and bisdemethoxycurcumin have also been isolated from *Curcuma mangga*,[2] *Curcuma zedoaria*,[3] *Costus speciosus*,[4] *Curcuma xanthorrhiza*,[4] *Curcuma aromatica*,[5] *Curcuma phaeocaulis*,[5] *Etlingera elatior*,[6] and *Zingiber cassumunar*[7] (Figure 1; see Table 1). Curcumin is the phytochemical that gives a yellow color to turmeric and is now recognized as being responsible for most of the therapeutic effects. It is estimated that 2–5% of turmeric is curcumin. Curcumin was first isolated from turmeric in 1815, and the structure was delineated in 1910 as diferuloylmethane. Most currently available preparations of curcumin contain approximately 77% diferuloylmethane, 18% demethoxycurcumin, and 5% bisdemethoxycurcumin. Curcumin is hydrophobic in nature and frequently soluble in dimethylsulfoxide, acetone, ethanol, and oils. It has an absorption maxima around 420 nm. When exposed to acidic conditions, the color of turmeric/curcumin turns from yellow to deep red, the form in which it is used routinely for various religious ceremonies.

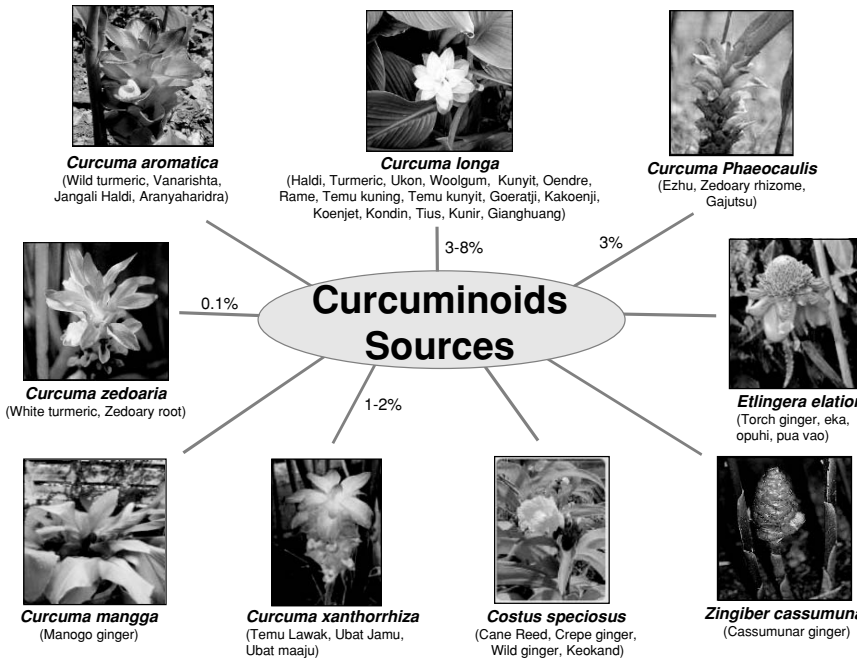


Figure 1. Sources of curcuminoids. (See also Plate 1 in the Color Plate Section.)

3. CURCUMIN ANALOGUES

As indicated earlier, turmeric contains three different analogues of curcumin (i.e., diferuloylmethane, also called curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Figure 2). Whether all three analogues exhibit equal activity is not clear. Although in most systems curcumin was found to be most potent,[8,9] in some systems bisdemethoxycurcumin was found to exhibit higher activity.[3,10] There are also suggestions that the mixture of all three is more potent than either one alone.[11,12]

When administered orally, curcumin is metabolized into curcumin glucuronide and curcumin sulfonate.[13] However, when administered systemically or intraperitoneally, it is metabolized into tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol. Tetrahydrocurcumin has been shown to be active in some systems[14–18] and not in others.[13,19] Whether other metabolites of curcumin exhibit biological activity is not known.

4. USES OF CURCUMIN

The use of turmeric for health purposes is nothing new. As a folklore medicine, its use has been documented in both Indian and Chinese cultures. The long list of uses

Table 1. List of various species of curcuma.

C. aeruginosa	*C. coriacea*	*C. meraukensis*	*C. rubricaulis*
C. albicoma	*C. decipiens*	*C. montana*	*C. rubrobracteata*
C. albiflora	*C. domestica*	*C. musacea*	*C. sessilis*
C. alismatifolia	*C. ecalcarata*	*C. mutabilis*	*C. sichuanensis*
C. amada	*C. ecomata*	*C.neilgherrensis*	*C. singularis*
C. amarissima	*C. elata*	*C. nilamburensis*	*C. soloensis*
C. americana	*C. erubescens*	*C. ochrorhiza*	*C. sparganifolia*
C. angustifolia	*C. euchroma*	*C. officinalis*	*C. speciosa*
C. aromatica*	*C. exigua*	*C. oligantha*	*C. spicata*
C. attenuata	*C. ferruginea*	*C. ornata*	*C. stenochila*
C. aurantiaca	*C. flaviflora*	*C. pallida*	*C. strobilifera*
C. australasica	*C. glans*	*C. parviflora*	*C. sulcata*
C. bakeriana	*C. glaucophylla*	*C. parvula*	*C. sumatrana*
C. bicolor	*C. gracillima*	*C. peethapushpa*	*C. sylvatica*
C. brog	*C. grahamiana*	*C. petiolata*	*C. sylvestris*
C. burttii	*C. grandiflora*	***C. phaeocaulis****	*C. thalakaveriensis*
C. caesia	*C. haritha*	*C. pierreana*	*C. thorelii*
C. cannanorensis	*C. harmandii*	*C. plicata*	*C. trichosantha*
C. caulina	*C. heyneana*	*C. porphyrotaenia*	*C. vamana*
C. careyana	*C. inodora*	*C. prakasha*	*C. vellanikkarensis*
C. ceratotheca	*C. latiflora*	*C. pseudomontana*	*C. viridiflora*
C. chuanezhu	*C. latifolia*	*C. purpurascens*	*C. wenchowensis*
C. chuanhuangjiang	*C. leucorhiza*	*C. purpurea*	*C. wenyujin*
C. chuanyujin	*C. leucorrhiza*	*C. raktakanta*	***C. xanthorrhiza****
C. cochinchinensis	*C. loerzingii*	*C. ranadei*	*C. yunnanensis*
C. codonantha	***C. longa****	*C. reclinata*	*C. zanthorrhiza*
C. coerulea	*C. longiflora*	*C. rhabdota*	***C. zedoaria****
C. colorata	*C. longispica*	*C. rhomba*	*C. zerumbet*
C. comosa*	*C. lutea*	*C. roscoeana*	
C. cordata	*C. malabarica*	*C. rotunda*	
C. cordifolia	***C. mangga****	*C. rubescens*	

Note: Curcuma is indicated by C.
*Curcuminoids have been isolated from the plant indicated in bold.
Source: Modified from http://en.wikipedia.org/wiki/Curcuma.

include antiseptic, analgesic, anti-inflammatory, antioxidant, antimalarial, insect-repellant, and other activities associated to turmeric.[4,20–27] (Figure 3). Perhaps one of the most often prescribed uses is for wound-healing.[28] This activity is well known to people from the Indian subcontinent. Modern research has provided considerable evidence, and the mechanism by which turmeric/curcumin could accelerate wound-healing has been described.[29–36]

It is now well recognized that most chronic diseases are the result of dis-regulated inflammation,[37,38] Turmeric has been traditionally described as an anti-inflammatory agent. Recent scientific evidence has indeed demonstrated that turmeric, and curcumin in particular, exhibits potent anti-inflammatory activities as determined by a wide variety of systems.[39–49] Therefore, it is not too surprising that turmeric displays activities against a variety of diseases. Because curcumin also exhibits potent antioxidant activity, whether the anti-inflammatory activity of curcumin is mediated through its antioxidant mechanism is not clear. Since most

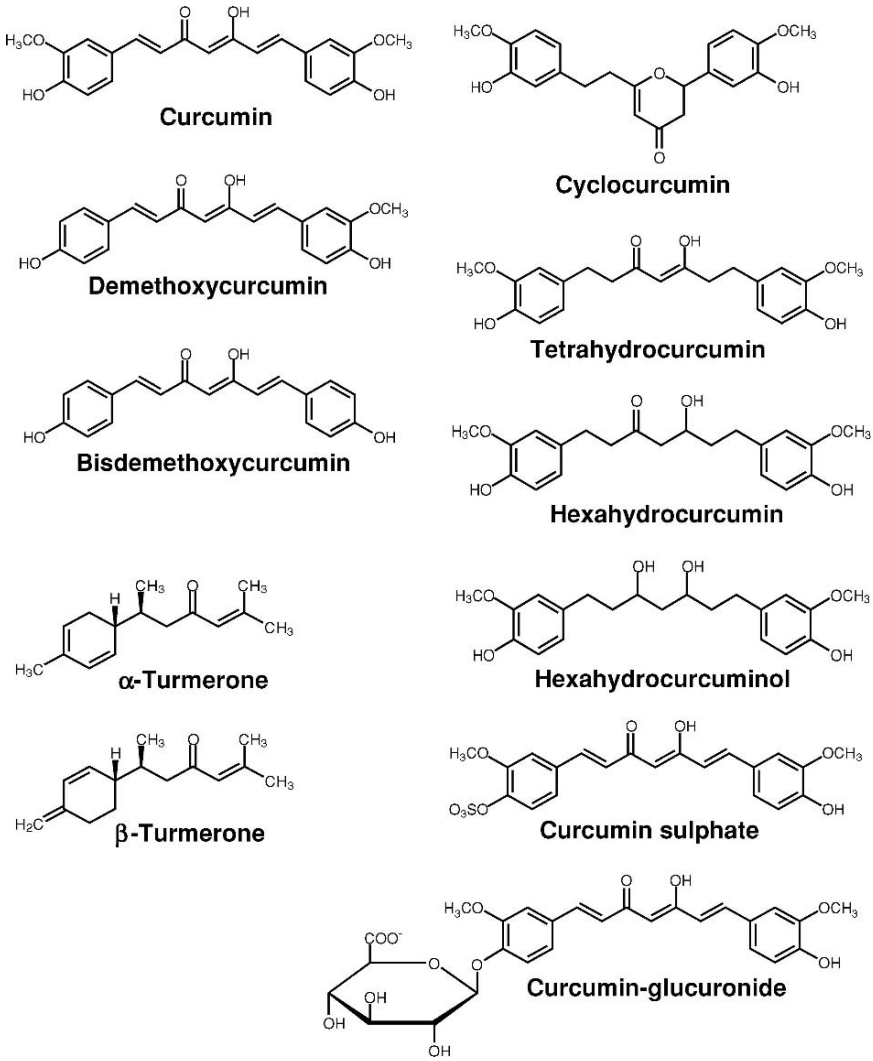


Figure 2. Chemical structures of curcumin and its analogues.

well-characterized antioxidants do not exhibit anti-inflammatory activity, it is unlikely that the anti-inflammatory activity of curcumin is due to its antioxidant activity.

5. MOLECULAR TARGETS OF TURMERIC/CURCUMIN

Most molecular targets established in modern biology were discovered within the last three decades. The effect of curcumin on most of these targets has

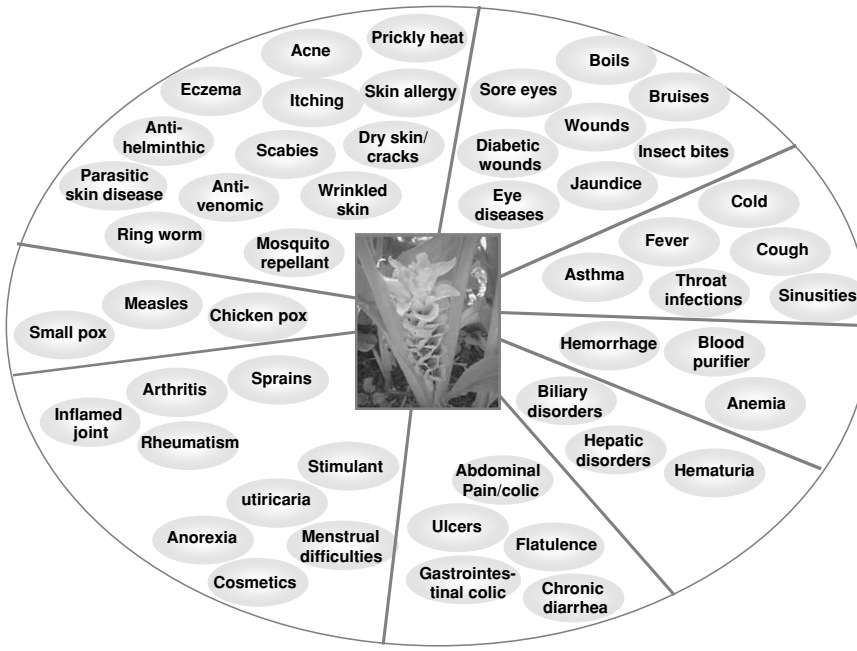


Figure 3. Traditional uses of curcmin. (See also Plate 2 in the Color Plate Section.)

been examined[10,12,45,50–201] (Figure 4). The results have revealed that curcumin can modulate several different transcription factors,[50–96,113,114] cytokines,[45,97–112] growth factors,[202–215] kinases,[115–128] and other enzymes.[91,129–159] Although most diseases are caused by dysregulated inflammation, to find a safe and efficacious anti-inflammatory agent is a real challenge in modern medicine. Steroids are perhaps the best known anti-inflammatory agents. However, there are numerous side effects associated with them. In addition to steroids, numerous nonsteroidal antiinflamatory drugs (NSAIDs) have been discovered within the last century, and these include salicylates, ibuprofen, sulindac, phenylbutazone, naproxen, diclofenac, indomethacin, and coxibs.[216] Experience over the years has indicated that most of these NSAIDs are associated with a constellation of side effects. Perhaps the best example is the cardiovascular system-related side effects recently identified with most coxibs.[217–219] Although the intake of such anti-inflammatory agents can be justified for chronic conditions, they are not appropriate as chemopreventive agents under normal conditions, because that purpose requires long periods of time. Thus, there is a great need for safer and efficacious anti-inflammatory agents.

Numerous lines of evidence suggest that curcumin is a potent anti-inflammatory agent (see Figure 5). First, curcumin suppresses the activation of the transcription factor NF–κB, which regulates the expression of pro-inflammatory gene products.[50–81] Second, curcumin downregulates the expression of COX-2, an

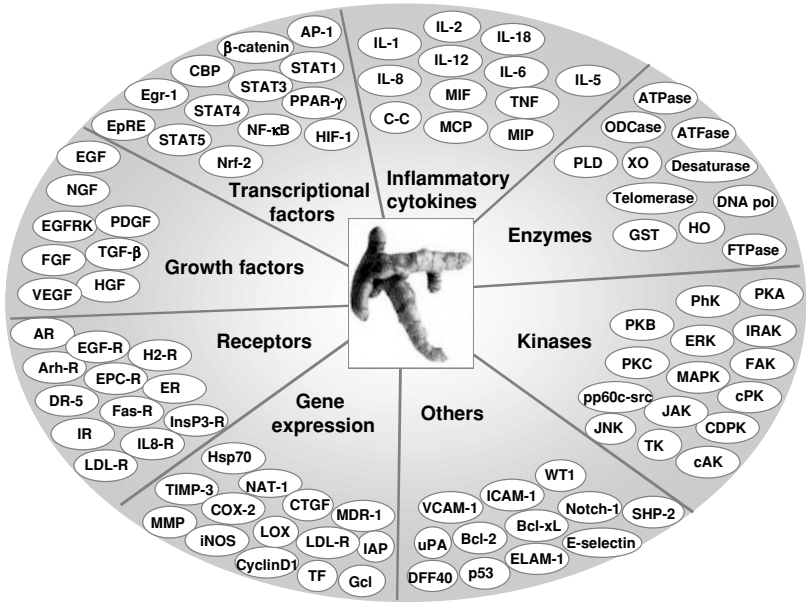


Figure 4. Molecular targets of curcumin. Abbreviations used: NF-κB, nuclear factor-κB; AP-1, activating protein-1; STAT, signal transducers and activators of transcription; Nrf-2, nuclear factor erythroid 2-related factor; Egr-1, early growth response gene-1; PPARγ, peroxisome preoliferator-activated receptor-γ; CBP, CREB-binding protein; EpRE, electrophile response element; CTGF, connective tissue growth factor; EGF, epidermal growth factor; EGFRK, EGF receptor-kinase; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; NGF, nerve growth factor; PDGF, platelet-derived growth factor; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; AR, androgen receptor; Arh-R, aryl hydrocarbon receptor; DR-5, death receptor-5; EGF-R, EGF-receptor; EPC-R, endothelial protein C-receptor; ER-α, estrogen receptor-α; Fas-R, Fas receptor; H2-R, histamine (2)-receptor; InsP3-R, inositol 1,4,5-triphosphate receptor; IR, integrin receptor; IL-8-R, interleukin-8-receptor; LDL-R, low-density lipoprotein-receptor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase-3; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; LOX, lipoxygenase; Gcl, glutamate-cysteine ligase; NAT, arylamine *N*-acetyltransferases; IAP, inhibitory apoptosis protein; HSP-70, heat shock protein 70; MDR, multidrug resistance; TNF-α, tumor necrosis factor-α; IL, interleukin; MCP, monocyte chemoattractant protein; MIF, migration inhibition protein; MIP, macrophage inflammatory protein; cAK, autophosphorylation-activated protein kinase; CDPK, Ca^{2+}-dependent protein kinase; cPK, protamine kinase; ERK, extracellular receptor kinase; FAK, focal adhesion kinase; IARK, IL-1 receptor-associated kinase; JAK, janus kinase; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; PhK, phosphorylase kinase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; pp60c-src, a nonreceptor protein tyrosine kinase c-Src, cellular src kinase; TK, protein tyrosine kinase; FPTase, farnesyl protein transferase; GST, gluthathione-*S*-transferase; HO, hemeoxygenase; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; ELAM-1, endothelial leukocyte adhesion molecule-1; Bcl-2, B-cell lymphoma protein 2; SHP-2, Src homology 2 domain-containing tyrosine phosphatase 2, uPA, urokinase-type plasminogen activator, DFF40; DNA fragmentation factor, 40-kd subunit. (See also Plate 3 in the Color Plate Section.)

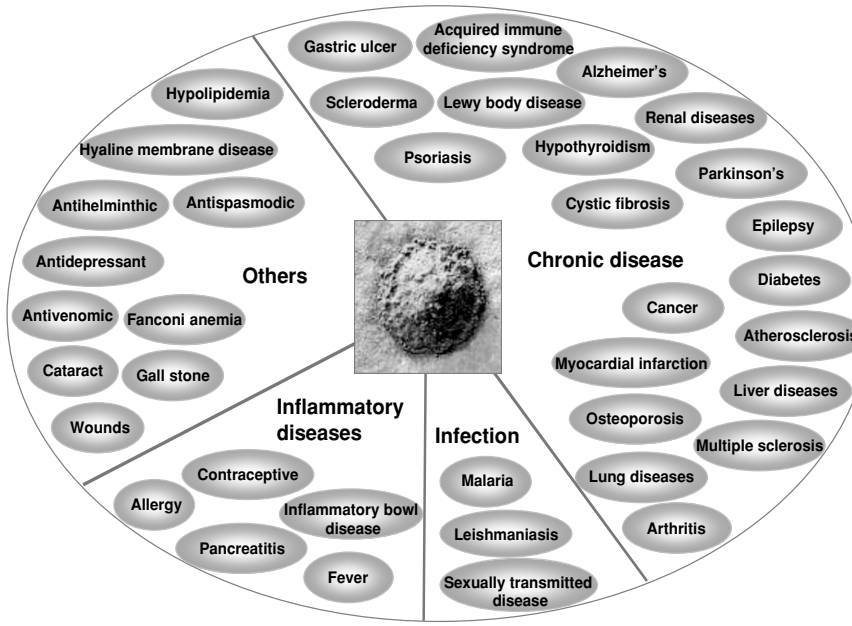


Figure 5. Potential uses of curcumin based on modern technology. (See also Plate 4 in the Color Plate Section.)

enzyme linked with most types of inflammations.[75,177–181,183] Third, curcumin inhibits the expression of another pro-inflammatory enzyme, 5-LOX.[177,182–184] Additionally, curcumin has been shown to bind to the active site of 5-LOX and inhibit its activity[183] Fourth, curcumin downregulates the expression of various cell surface adhesion molecules that have been linked with inflammation.[220–222] Fifth, curcumin downregulates the expression of various inflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and chemokines.[45,97–112] Sixth, curcumin has been shown to inhibit the action of TNF, one of the most pro-inflammatory cytokines.[97–100] Seventh, curcumin is a potent antioxidant, which might contribute to its anti-inflammatory action.[16,19,31,159,223–279] All of this recent evidence confirms the anti-inflammatory action of curcumin, known for thousands of years. Its pharmacological safety combined with its anti-inflammatory action, makes it an ideal agent to explore for preventive and therapeutic situations.

Whereas pro-oxidants are considerd mediators of numerous diseases, antioxidants are generally believed to delay or halt the disease. However, this paradigm is not always valid, as most cytokines mediate their effects through pro-oxidant mechanisms. Reactive oxygen species (ROS) also play an important role in cell-mediated cytotoxicity (CMC) of the immune system. Numerous reports indicate that curcumin could mediate both pro-oxidant and antioxidant roles. First, curcumin could induce the expression of ROS,[8,280–282] which plays an important role in the antiproliferative effects of this molecule.[283] Second, curcumin binds

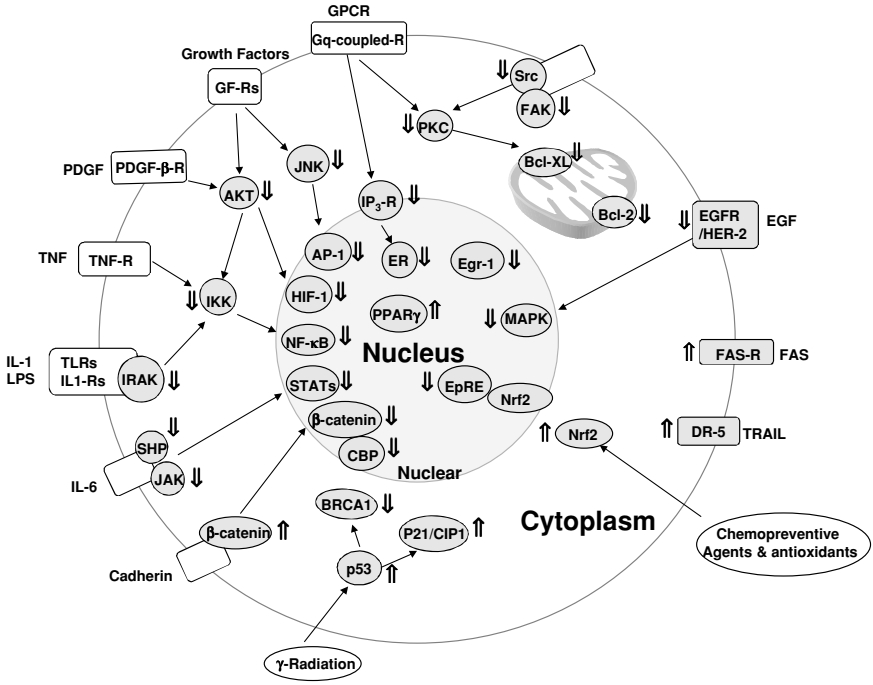


Figure 6. Signaling pathway modulated by curcumin. Intermediates upregulated by curcumin are indicated as ⇑ and those downregulated by curcumin are indicated as ⇓.

thioredoxin reductase (TR) and converts this enzyme to NADPH oxidase, thus leading to the production of ROS.[284] Because TR is overexpressed in tumor cells,[285–287] curcumin kills tumor cells through this mechanism. Third, curcumin suppresses lipid peroxidation.[224,226–228,232,234,238,252,256,264,265,268,288,289] Fourth, curcumin increases the expression of intracellular glutathione.[139,140,142,143,146,290–294] Fifth, curcumin could also play an antioxidant role through its ability to bind iron.[229] All of these reports combined suggest the ability of curcumin to modulate the redox status of the cells. That curcumin can modulate the cellular action of various growth factors and cytokines has also been demonstrated (Figure 6). First, curcumin has been shown to downregulate the effect of epidermal growth factor (EGF) through downregulation of expression and activity of EGF receptors (EGFR).[203,210–212] Second, curcumin has been shown to downregulate the activity of human EGFR-2 (called HER2/neu),[127] a growth factor receptor closely linked with cancer of the breast, lung, kidney, and prostate. Third, curcumin suppresses the action of interleukin (IL)-6 through the downregulation of STAT3 activation.[296] Fourth, curcumin modulates the action of TNF, a growth factor for tumor cells.[297] Fifth, curcumin negatively regulates the action of IL-2,[298] a growth factor for T cells. Thus, curcumin can affect the action of a wide variety of growth factors.[202–215]

Angiogenesis is a process of vascularization of the tissue, which is critical for the growth of solid tumors. Numerous molecules have been linked with angiogenesis. These include vascular endothelial growth factor (VEGF), COX-2, fibroblast growth factor (FGF), and TNF. Evidence suggests that curcumin could suppress angiogenesis.[113,205,208,299–303] Curcumin includes its ability to downregulate the expression of VEGF.[208] Likewise, it downregulates FGF-mediated angiogenesis.[205] Curcumin was found to negatively regulate the expression of COX-2[74,177–181] and suppresses both the expression and action of TNF.[97–100]

6. CURCUMIN RECEPTORS

Receptors are cellular proteins to which a molecule binds, leading to secondary cellular responses. Whether there are any authentic receptors for curcumin is not known. However, numerous molecules to which curcumin binds have been identified. These include serum albumin,[304,305,306] 5-LOX,[183,307] xanthine oxidase,[159] thioredoxin reductase,[284] iron,[295] COX-2,[308] IKK,[309] *p*-glycoprotein,[310,311] GST,[291] PKA,[115] PKC.[115] cPK,[115] PhK,[115] autophosphorylation-activated protein kinase,[115] pp60c-src tyrosine kinase,[115] Ca^{2+}-dependent protein kinase (CDPK),[116] Ca^{2+}-ATPase of sarcoplasmic reticulum,[131] aryl hydrocarbon receptor,[186] rat river cytochrome p450s,[291] Topo II isomerase,[312] inositol 1,4,5-triphosphate receptor,[313] and glutathione.[143]

7. DISEASE TARGETS OF CURCUMIN

Extensive research within the last half a decade has revealed that curcumin has potential against a wide variety of diseases, both malignant and nonmalignant (see Figure 5). The potential of curcumin, however, has not been systematically examined through the modern multicenter, randomized, double-blind, placebo-controlled clinical trials.[314–335] Its potential in humans is indicated either through preclinical studies, some pilot studies in humans, anecdotal studies in patients, or epidemiological studies. Curcumin has been shown to exhibit activity against numerous inflammatory diseases, including pancreatitis,[100,214,261,336,337] arthritis,[105,338–341] inflammatory bowel disease (IBD),[332] colitis,[342–344] gastrititis,[345,346] allergy,[99,347,348] and fever,[349,350] possibly through the downregulation of inflammatory markers, as indicated earlier. The effect of curcumin against various autoimmune diseases has also been demonstrated; they include scleroderma,[351] psoriasis,[352]multiple sclerosis,[111,353] and diabetes.[354–362] Again, these effects of curcumin are through the regulation of pro-inflammatory signaling.

Although once thought to be distinct, the molecular targets for both the prevention and therapy of cancer are now considered the same,[363,364]. Numerous lines of evidence suggest the potential of curcumin against various types of cancer[11,56,76,83,95,145,153,155,273,283,298,309,365–462] (see Table 2). First,

Table 2. Chemopreventive and anticancer effects of curcumin.

Skin
External cancerous lesion[405]
Human basal cell carcinoma[469]
Human melanoma[412–414]
Human epidermal carcinoma[415]
Prevention from
7,12-dimethylbenz[a]anthracene[11,406]
Prevention from azoxymethanol[407]
Prevention from benz[a]pyrene and
12-O-tetradecanoylphorbol-13-acetate[408]
Prevention from 12-O-tetradecanoylphorbol-13-acetate[153,155,409]
Prevention from
12-O-tetradecanoylphorbol-13-acetate- and
7,12-dimethylbenz[a]anthracene[410]

Oral
Prevention from
methyl-(acetoxymethyl)-nitrosamine[416]
Prevention from 4-nitroquinoline 1-oxide[417]
Prevention from
7,12-dimethylbenz[a]anthracene[418–420]

Esophageal
Prevention from
N-nitrosomethylbenzylamine[421]

Forestomach
Prevention from benzo[a]pyrene[406,422,423]
Prevention from
N-methyl-N'-nitro-N-nitrosoguanidine[424]

Intestine
Prevention from Min/+ mouse
(a model of familial adenomatous polyposis)[425,426]

Colon
Colon adeno carcinoma[95,435–440]
Prevention from azoxymethane[427–433]
Prevention from 1,2-dimethylhydrazine dihydrochrolide[434]

Mammary gland
Prevention from 7,12-dimethylbenz[a]anthracene[11,427,441–443]
Prevention from diethylstilbestrol[444]
Prevention from radiation[365,455]

Liver
Human hepatoblastoma[371,462]
Prevention from diethylnitrosamine[366,367,369]
Prevention from N-nitrosodiethylamine and phenobarbital[370]

Prostate
Prevention from 3,2'-dimethyl-4-aminobiphenol (DMAB) and 2-amino-1-methylimidazo[4,5-b]pyridine (PhIP)[372]

Blood and Bone Marrow
Human leukemia[145,273,373–379]
T-lymphocyte[298,380,381]
Rat thymocytes[382]
Rat histhymocytoma[283]
B-cell lymphoma[56,383,384]
B-cell non-Hodgkin's lymphoma[385,386]
Burkitt's lymphoma[387]
Human multiple myeloma[83,309,388]
Primary effusion lymphoma[389]

Brain
Neuroblastoma[390,391]
Ehrlich's ascites carcinoma[456,480]
Astrocytoma[393]

Breast
Breast carcinoma [394–399]

Gatrointestinal
Gastric signet ring carcinoma[400]

Head and Neck
Head and neck squamous cell carcinoma[76,200,401]

Lung
Human lung[402,447]

Pancreas
Pancreatic carcinoma[403]

Ovarian
Human ovarian[404]

curcumin has been shown to suppress the proliferation of a wide variety of tumor cells through the downregulation of antiapoptotic gene products, activation of caspases, and induction of tumor suppressor genes such as $p53$.[95,145,283,298,313,351,373–384,389–393,396,397,399–403,411,412,415,435–440,463–499]