

THE ENZYMES

Natural Products and Cancer Signaling:
Isoprenoids, Polyphenols and Flavonoids

Edited by
S. Zahra Bathaie
Fuyuhiko Tamanoi

VOLUME XXXVI





VOLUME THIRTY SIX

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Edited by

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Academic Press is an imprint of Elsevier



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32 Jamestown Road, London NW1 7BY, UK
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
225 Wyman Street, Waltham, MA 02451, USA
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

First edition 2014

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ISBN: 978-0-12-802215-3

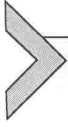
ISSN: 1874-6047

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PREFACE

Anticancer activities of compounds from natural resources have been documented extensively in recent decades. However, molecular mechanisms of the action of these compounds need to be further elucidated. In particular, it will be important to understand the signaling pathways targeted by these natural compounds. We have realized that various recent activities have started to shed new lights into this problem. To capture these developments, we decided to put together a volume describing recent studies concerning the role of natural compounds in cancer therapy and cancer prevention. We believe that compiling the knowledge on elucidating targets of natural compounds is important, as it may provide hints about future developments such as possible combination therapies.

In this volume, we described studies on isoprenoids, polyphenols, and flavonoids. In future volumes, we plan to cover other classes of natural products.

We are very grateful to the authors for their effort in providing excellent and informative chapters in a timely fashion. We also thank Mary Ann Zimmerman and Helene Kabes of Elsevier for their guidance and encouragement during the preparation of this volume.

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September 2014

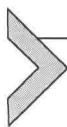
CONTENTS

<i>Contributors</i>	ix
<i>Preface</i>	xiii
1. Introduction	1
S. Zahra Bathaie and Fuyuhiko Tamanoi	
References	6
2. Perillyl Alcohol (Monoterpene Alcohol), Limonene	7
Shahla Shojaei, Amir Kiumarsi, Adel Rezaei Moghadam, Javad Alizadeh, Hassan Marzban, and Saeid Ghavami	
1. Introduction	8
2. Perillyl Alcohol	12
3. Limonene	16
4. Concluding Remarks	25
Acknowledgment	26
References	26
3. Ganoderic Acid and Lucidenic Acid (Triterpenoid)	33
Chin-Lin Hsu and Gow-Chin Yen	
1. Introduction	34
2. Lucidenic Acids and Ganoderic Acids from <i>Ganoderma</i> Species	35
3. Biological Functions of Lucidenic Acids and Ganoderic Acids	43
4. Pharmacokinetics of Ganoderic Acids	50
5. Conclusion	51
References	52
4. Anticancer Effect and Molecular Targets of Saffron Carotenoids	57
S. Zahra Bathaie, Azam Bolhassani, and Fuyuhiko Tamanoi	
1. Introduction	59
2. Anticancer Effect of Saffron and Its Carotenoids	59
3. Comparing the Efficacy of Crocetin, Crocin, and Other Components	60
4. Liposome Formulation of Saffron Compounds	64
5. Effect of Crocetin and Crocin on Macromolecule Synthesis and Structure	66
6. Effects on Cell Cycle, Apoptosis, and Signaling Pathways	68

7. Role of Saffron Components on Chemoprevention	71
8. Molecular Mechanisms Involved in the Protective Effect of Saffron Components against Various Damages in Different Tissues	73
9. Antioxidant and Anti-inflammatory Effects of Saffron	76
10. Safety	78
11. Other Mechanisms	78
12. Conclusions	79
References	79
5. Zerumbone from Ginger (Monoterpenoid)	87
Yoichi Matsuo and Hiromitsu Takeyama	
1. Introduction	88
2. Characteristic Feature	89
3. Target Pathways by Zerumbone	89
4. Nuclear Factor-Kappa B	91
5. Future Perspectives	91
References	92
6. Research Progress on Natural Triterpenoid Saponins in the Chemoprevention and Chemotherapy of Cancer	95
Jun-Rong Du, Fang-Yi Long, and Chu Chen	
1. Introduction	96
2. Triterpenoid Saponins in the Prevention and Therapy of Cancers	97
3. Anticancer Properties and Molecular Mechanisms of Triterpenoid Saponins	98
4. Structure–Activity Relationships of Anticancer Activities of Triterpenoid Saponins	121
5. Clinical Studies	122
6. Summary and Perspectives	123
References	124
7. Neem Limonoids as Anticancer Agents: Modulation of Cancer Hallmarks and Oncogenic Signaling	131
Siddavaram Nagini	
1. Introduction	132
2. Cytotoxicity of Neem Limonoids	133
3. Neem Limonoids and Hallmarks of Cancer	136
4. Oncogenic Signaling	140

5. Conclusions and Future Perspectives	142
References	143
8. Curcumin: A Potent Modulator of Multiple Enzymes in Multiple Cancers	149
Adeeb Shehzad, Raheem Shahzad, and Young Sup Lee	
1. Introduction	150
2. Structure–Activity Relationship of Curcumin	152
3. Curcumin Binds and Modulates Multiple Enzymes	153
4. Curcumin Binds and Modulates PKs	160
5. Curcumin Directly Binds and Modulates Protein Reductases	162
6. Others	163
7. Curcumin Clinical Trials in Cancer	164
8. Future Perspectives	165
Acknowledgment	166
References	166
9. Molecular Targets of Honokiol: A Promising Phytochemical for Effective Cancer Management	175
Courey Averett, Sumit Arora, Haseeb Zubair, Seema Singh, Arun Bhardwaj, and Ajay P. Singh	
1. Introduction	176
2. Honokiol: Structure–Activity Relationship	177
3. Anticancer Effect of Honokiol	178
4. Molecular Targets of Honokiol	180
5. Pharmacokinetics of Honokiol	187
6. Conclusion and Future Outlook	188
Acknowledgments	189
References	189
10. Effects of Tea Catechins on Cancer Signaling Pathways	195
Chung S. Yang, Hong Wang, Jayson X. Chen, and Jinsong Zhang	
1. Introduction	196
2. Chemistry, Bioavailability, and Biotransformation of Tea Catechins	197
3. Inhibition of Tumorigenesis by Tea Catechins in Animal Models and Possible Mechanisms	199
4. Biochemical Activities of Tea Catechins	202

5. Modulating Signaling Pathways and Cell Functions	207
6. Issues in Extrapolating Studies <i>In Vitro</i> to Situations <i>In Vivo</i>	213
7. Concluding Remarks	214
Acknowledgments	215
References	215
 <i>Author Index</i>	 223
<i>Subject Index</i>	253



Introduction

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Contents

References

6

Abstract

Natural products and phytochemicals have extensively attracted for their various biological effects, especially for both treatment and prevention of cancer. In this book, we try to introduce various phytochemicals as cancer therapy targets with emphasize on their effect on signal transduction pathways and their molecular targets.

Natural products are chemical substances produced by living organisms and have distinctive biological and pharmacological effects, even if they can be prepared by total synthesis. These are foreign to humans (i.e., xenobiotics) and are subject to the same pharmacological issues encountered by synthetic therapeutic agents [1].

Plants and microbes are two important sources of natural products. Antibiotics are the oldest biologically active compounds separated from microbes and used as drug to cure various human diseases, especially cancer.

Among the wide range of biologically active compounds obtained from different sources in nature, medicinal uses of plants possibly are the oldest one and came back to the ancient time, as they used by various nations. Historically, various parts of the plants, such as fruit, flower, leaves, stalks, root, seed, and even the whole plant, have been used as the home remedy. Different methods have also been used for preparation of the herbal remedy; they include preparation of the pills, capsules, or sachets from the powder; decoctions (boiled); infusion; extraction with water or oil; and so on [2]. All of these preparations have been used orally. However, some preparations may have the topical application. Thus, they can be used for inhalation therapy or in a mixture as the skin cream. In all of the above-mentioned

methods, the main goal is the efficient absorption of the effective ingredient(s) in the body.

Nowadays, targeted therapy or molecularly targeted therapy, especially in cancer treatment, has been considered to accomplish more effective treatment with less harmful effect to normal cells. In this regard, scientists try to use the more effective ingredient of the herbals, instead of the crude extract to achieve the more powerful therapy with no or minimum side effect. Therefore, fractionation, purification, and characterization of the active components have been extensively considered.

Phytochemicals (from the Greek word *phyto*, meaning plant) are compounds found in plants. They are biologically active and provide health benefits for humans. These chemicals have metabolic or protective role in their own plants, but may exert the same or other effects in other organisms like animal or human bodies.

Table 1.1 shows the overall classification of phytochemicals according to their chemical structure, biological activity, and plant sources. Different chapters of this book reviewed the mechanism(s) of the anticancer effect of some of these phytochemicals.

Various biological or pharmacological activities have been reported for phytochemicals. Some of them include antimicrobial, antiviral, or antifungal effects; antioxidant activity or activation of the antioxidant defense system; modulation of the detoxifying enzymes; stimulation or suppression of the immune system; decrease of platelet aggregation; modulation of hormone metabolism; and regulation of the metabolism of the building blocks in the body.

Chemoprevention and anticancer property are two novel approaches emphasizing the prevention or delay of carcinogenesis, or treatment of cancer by means of natural products through pharmacologic, biologic, and even nutritional intervention. This involves the discovery and characterization of the phytochemicals as a new drug with specific effect on cell cycle proteins, growth factors, or hormone receptors, and/or specific inhibitory or activatory effect on specific enzymes. Chemotherapeutic and chemoprevention by targeting key components of the apoptosis pathways, cell cycle checkpoints, autophagy regulation, ER stress response, and protein folding targets are the main goal of the new drug design approaches (Fig. 1.1).

Targeting of the tumor microenvironment, more particularly inflammatory mediators and reactive oxygen/nitrogen species; upregulation of intercellular communication through gap junction or tight junction; regulation of upstream kinases of intracellular signaling cascades or downstream transcription factors; elimination of endogenous and environmental

Table 1.1 Family and Chemical Structure of Phytochemicals Found in Plants

Row	Family	Chemical Structure	Component	Plant Name
1	Isoprenoids or terpenoids	Monoterpenoids	Zingerone or vanillylacetone	Ginger
2			Terpineol	
3			Picrocrocin	Saffron
4		Diterpenoids	Taxol (or paclitaxel)	<i>Taxus brevifolia</i>
5		Triterpenoids	Saponins	Many plants
			Ganoderic acid	<i>Ganoderma</i> mushrooms
			Lucidenic acid	<i>Ganoderma</i> mushrooms
			Ursolic acid	Apple, basil, bilberries
6		Tetraterpenoids or carotenoids	Beta-carotene	Carrot
7			Lycopene	Tomato
			Lutein	Spinach, kale, and yellow carrot
			Crocin and crocetin	Saffron
8		Tetranortriterpenoids	Limonoids	Citrus fruits
9		Steroids (phytosterols)	Withanolide	Tomatillo
10	Phenolics and polyphenols	Curcuminoid	Curcumin	Turmeric
11		Stilbenoid	Resveratrol	Skin of red grapes
12		Lignan	Honokiol	Magnolia
13		Chalconoids	Chalcones	
			Geranyl chalcone Geranylgeraniol	
14		Tannins		Pomegranates, persimmon, berries, nuts

Continued

Table 1.1 Family and Chemical Structure of Phytochemicals Found in Plants—cont'd

Row	Family	Chemical Structure	Component	Plant Name
15	Flavonoid-polyphenolics	Quercetin		Radish leaves, dill, red onion
16		Kaempferol		Tea, broccoli, grapefruit
17		Flavan-3-ols	Catechins	Green tea
18	Flavonoids	Flavones	Apigenin, chrysin, luteolin	Parsley, celery, and citrus peels
		Flavanones	Eriodictiol, hesperitin	Citrus fruits
19		Isoflavonoids	Genistein	Fava beans, soybeans
20		Licoflavanone		<i>Glycyrrhiza glabra</i>
21	Anthocyanidins	Cyanidin		Grapes, bilberry, blackberry, blueberry, cherry
22	Polycyclic compounds	Quinoline alkaloid	Camptothecin	Camptotheca, happy tree
23	Aromatic compounds	Aromatic acids (hydroxycinnamates)	Cinnamic acid	Cinnamon
24			Caffeic acid	Basil, apple
25			Coumarin	Citrus fruits
26		Aromatic aldehyde	Safranal	Saffron
27	Glucosinolates	Isothiocyanates	Allyl isothiocyanate	Mustard, radish, horseradish
28	Vanilloids	Phenolic aldehyde	Vanillin and derivatives (vanillic acid, vanillyl alcohol, etc.)	Vanilla bean
			Capsaicin	Chili peppers
29	Organosulfurs	Allylic sulfurs	Allicin	Garlic
30			Diallyl disulfide	
31	Thiosulfates			Leek
32	Aromatic heterocyclic	Indole alkaloids		Calabar bean seed, rye and related cereals
		Ergot alkaloids		
		Monoterpenoid alkaloids		

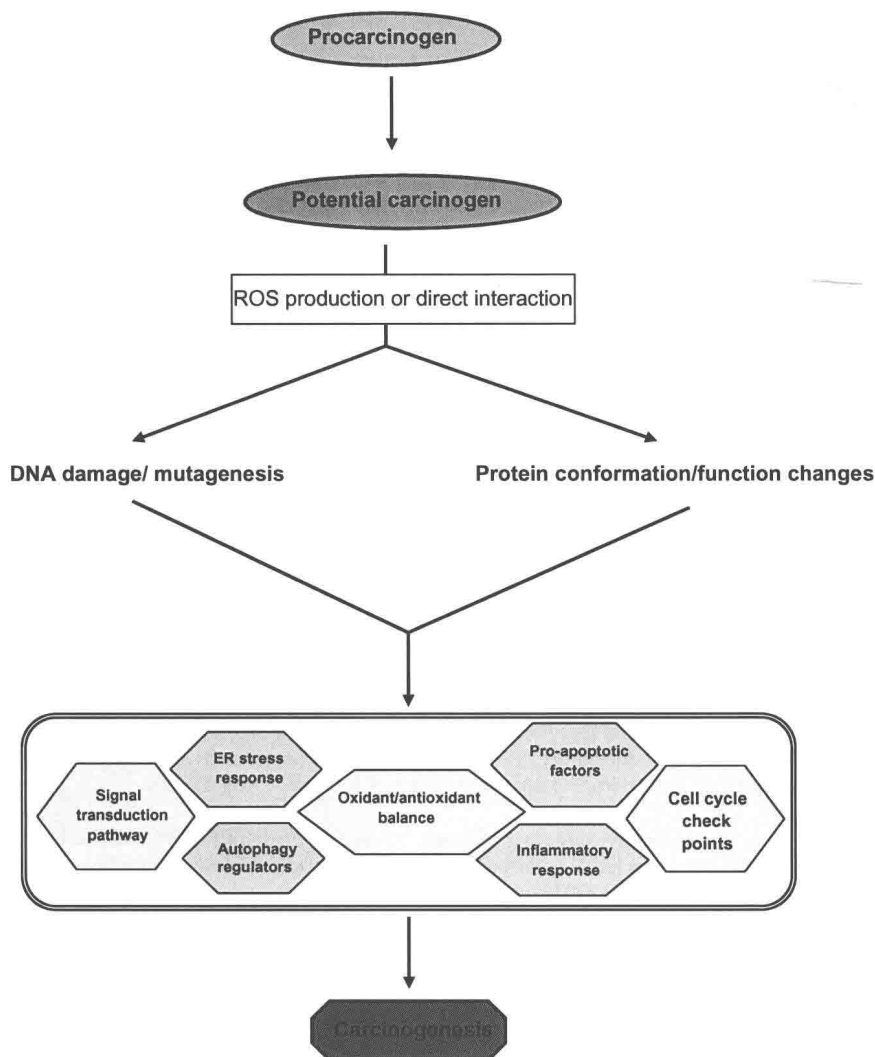


Figure 1.1 The process of carcinogenesis from beginning. Various phytochemicals and drugs can inhibit any step(s), which is extensively discussed in the chapters of this book.

carcinogens; and/or reduction of angiogenesis are some proposed chemopreventive strategies by means of pharmacological or nutritional factors.

Among the mechanisms mentioned in Fig. 1.1, reactive oxygen species (ROS) production (the cellular distortion in the balance of oxidant/antioxidant) is the most important in both carcinogenesis and killing of cancer cells. A set of 13 p53-induced genes (*PIG* genes) have a key role in the reactions