# THE ENZYMES

## Natural Products and Cancer Signaling: Isoprenoids, Polyphenols and Flavonoids

Edited by
S. Zahra Bathaie
Fuyuhiko Tamanoi

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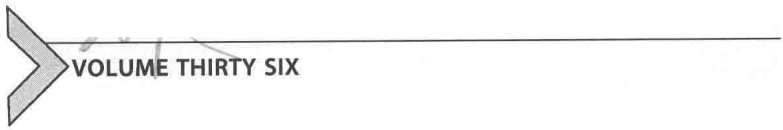


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## Natural Products and Cancer Signaling: Isoprenoids, Polyphenols and Flavonoids

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## Natural Products and Cancer Signaling: Isoprenoids, Polyphenols and Flavonoids

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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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# CONTENTS

CHAPTER ONE

# Introduction

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## Contents



## 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

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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, antivirus, 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) | *Taxus brevifolia* |
| 5 | | Triterpenoids | Saponins | Many plants |
| | | | Ganoderic acid | *Ganoderma* mushrooms |
| | | | Lucidenic acid | *Ganoderma* 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<br>Geranyl chalcone<br>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 anion |
| 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 | | *Glycyrrhiza glabra* |
| 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 | | |

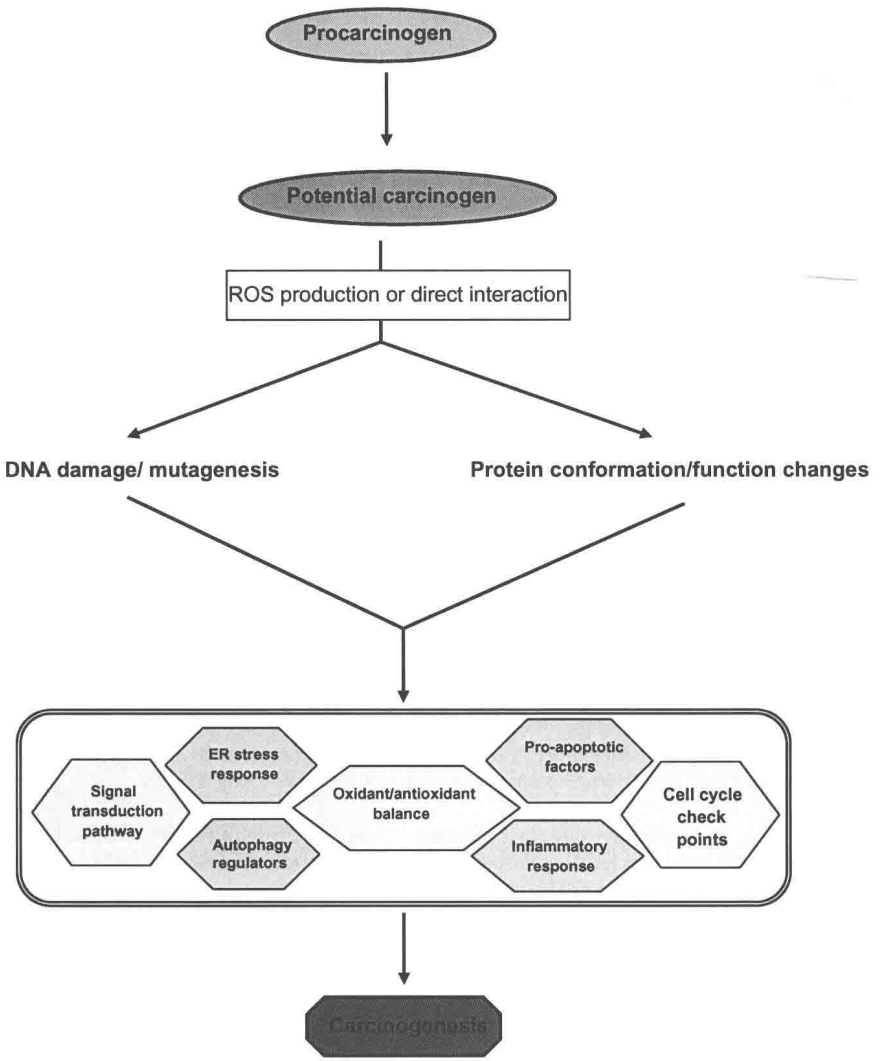


**Figure 1.1** The process of carcinogenesis from beginning. Various phytochemicals and drugs can inhibit any step(s), which is extensively discussed in the chapters of this book.

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