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Terpenoids As Therapeutic Drugs and Pharmaceutical Agents

Guangyi Wang, Weiping Tang, and Robert R. Bidigare

Summary

Terpenoids, also referred to as terpenes, are the largest group of natural compounds. Many terpenes have biological activities and are used for the treatment of human diseases. The worldwide sales of terpene-based pharmaceuticals in 2002 were approximately US $12 billion. Among these pharmaceuticals, the anticancer drug Taxol® and the antimalarial drug Artimesinin are two of the most renowned terpene-based drugs. All terpenoids are synthesized from two five-carbon building blocks. Based on the number of the building blocks, terpenoids are commonly classified as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), and sesterterpenes (C_{25}). These terpenoids display a wide range of biological activities against cancer, malaria, inflammation, and a variety of infectious diseases (viral and bacterial). In last two decades, natural-product bioprospecting from the marine environment has resulted in hundreds of terpenoids with novel structures and interesting bioactivities, with more to be discovered in the future. The problem of supply is a serious obstacle to the development of most terpenoid compounds with interesting pharmaceutical properties. Although total chemical synthesis plays a less important role in the production of some terpenoid drugs, it has contributed significantly to the development of terpenoid compounds and terpene-based drugs by providing critical information on structure–activity relationships (SAR) and chiral centers as well as generating analog libraries. Semisynthesis, on the other hand, has played a major role in the development and production of terpenoid-derived drugs. Metabolic engineering as an integrated bioengineering approach has made considerable progress to produce some terpenoids in plants and fermentable hosts. Cell culture and aquaculture will provide a solution for the supply issue of some valuable terpenes from terrestrial and marine environments, respectively. Recent advances in environmental genomics and other "-omics" technologies will facilitate isolation and discovery of new terpenoids from natural environments. There is no doubt that more terpenoid-based clinical drugs will become available and will play a more significant role in human disease treatment in the near future.

Key Words: Natural products; bioactive terpenoids; biosynthesis; chemical synthesis; drug discovery and development; sustainable production.

1. Introduction

Natural products have played a significant role in human disease therapy and prevention *(1)*. More than 60% and 75% of the chemotherapeutic drugs for cancer and infectious disease, respectively, are of natural origin *(2)*. With more than 23,000 known compounds, terpenoids, also referred to as terpenes, are the largest class of natural products. Among this group, many interesting compounds are extensively applied in the industrial sector as flavors, fragrances, and spices, and are also used in perfumery

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and cosmetics products and food additives *(1,3,4)*. Many terpenes have biological activities and are used for medical purposes. For example, the antimalarial drug Artemisinin and the anticancer drug paclitaxel (Taxol®) are two of a few terpenes with established medical applications. Natural products continue to be one of the most important sources of lead compounds for the pharmaceutical industry. At the same time, more terpenes have been discovered as efficacious compounds in human disease therapy and prevention. In particular, marine chemists and biologists have identified many marine terpenes with promising potential for medical applications. For instance, eleutherobin and sarcodictyin A from the Australian soft coral *Eleutherobia* sp. *(5)* and the stoloniferan coral *Sarcodictyon roseum (6,7)*, respectively, exhibit potent antitumor activity against a variety of tumor cells. Therefore, terpenoids presumably will play an increasingly important role as therapeutic and preventative agents for human diseases. In this chapter, we review the status of terpenoids as potential pharmaceutical agents, with an emphasis on monoterpenes, sesquiterpenes, diterpenes, and sesterterpenes.

2. Biosynthesis of Terpenoids

Terpenoids show enormous chemical and structural diversity. However, their backbones are synthesized from only two five-carbon isomers: isopentenyl diphosphate (IPP, C_5) and its highly electrophilic isomer, dimethylallyl diphosphate (DMAPP, C_5). There are two known pathways for the biosynthesis of these two universal precursors (**Fig. 1**). Details on the progress of the elucidation of these two biosynthetic pathways are summarized in several excellent reviews *(4,8–17)*. From these two basic building blocks, a group of enzymes called prenyltransferases can synthesize linear prenyl diphosphates, which serve as the precursors for terpenoid biosynthesis. During biosynthesis, the active isoprene unit (IPP) is repetitively added to DMAPP or a prenyl diphosphate in sequential head-to-tail condensations catalyzed by the prenyltrans-ferases. The reaction starts with elimination of the diphosphate ion from an allylic diphosphate to form an allylic cation, which is attacked by the IPP molecule with stereospecific removal of a proton to form a new C-C bond and a new double bond in the product (**Fig. 2**) *(18)*. Through consecutive condensations of IPP with an allylic prenyl diphosphate, a prenyltransferase can synthesize a variety of products with fixed lengths and stereochemistry. The chain length of prenyl diphosphates ranges from geranyl diphosphate (GPP, C_{10}) to natural rubber, whose carbon chain length extends to several million *(18–20)*. All prenyltransferases require divalent metals such as Mg^{2+} or Mn^{2+} for catalysis. GPP synthase and farnesyl diphosphate (FPP, C_{15}) synthase catalyze condensation reactions with IPP and DMAPP to form GPP, a precursor to monoterpenes, and FPP, a precursor to sesquiterpenes, respectively *(21,22)*. Geranylgeranyl diphosphate (GGPP, C_{20}) synthase *(18,19)* and farnesylgeranyl diphospate (FGPP, C_{25}) *(23,24)* synthase use the same condensation reactions to synthesize GGPP, a precursor to diterpene, and FGPP, a precursor to sesterterpene, respectively (**Fig. 2**).

Terpene cyclases are responsible for the biosynthesis of the thousands of natural terpenoid compounds found in terrestrial and marine organisms. Terpenes are synthesized from linear prenyl diphosphates in the cyclization cascades mediated by terpenoid cyclases (also known as terpene synthases or isoprenoid synthases), which are known to catalyze the most complex chemical reactions known in chemistry and biology *(25–27)*. A terpenoid cyclase binds and chaperones a linear prenyl diphosphate

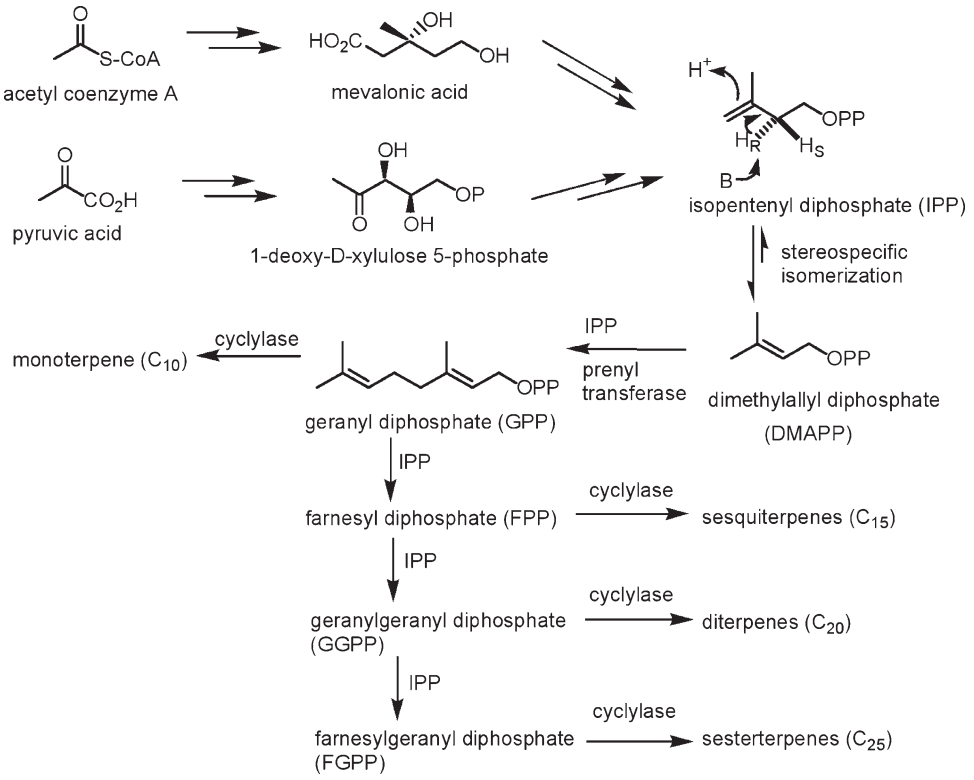

Fig. 1. Biosynthetic pathways of terpenes.

substrate through a precise and multistep cyclization cascade that is initiated by the generation and propagation of highly reactive carbocationic intermediates, which readily undergo dramatic structural rearrangements. The cyclase controls the reactions and provides a template for cyclization and rearrangement with stereochemical and regiochemical precision *(26–30)*. Over all, two-thirds of the substrate carbon atoms undergo changes in chemical bonding and/or hybridization to form a single, unique product *(27)*.

Variations in the number of isoprene unit repetitions, cyclization reactions, and rearrangements are primarily responsible for the chemical and structural diversity of terpenoids *(31)*. Many structurally distinct monocyclic and bicyclic terpenes arise from cyclization and rearrangement of GPP; the larger precursors FPP, GGPP, and FGPP give rise to an even greater variety of terpene carbon skeletons. The variety of ways in which these linear and cyclic skeletons can be arranged, results in the incredible structural diversity observed in nature. Many terpenes have carbacyclic ring systems and oxidized carbon chains such as alcohols and/or carbonyl groups. Some terpenoids have sugar moieties. The bicyclic and polycyclic ring systems with three- and four-membered rings appear commonly in terpenes *(9,13,32,33)*. Based on the number of five-carbon isoprene units in their linear precursor prenyl diphosphate, terpenoids are typically classified as C_5 hemiterpenes, C_{10} monoterpenes, C_{15} sesquiterpenes, C_{20} diterpenes, C_{25} sesterterpenes, and C_{30} triterpenes *(3,20)*.

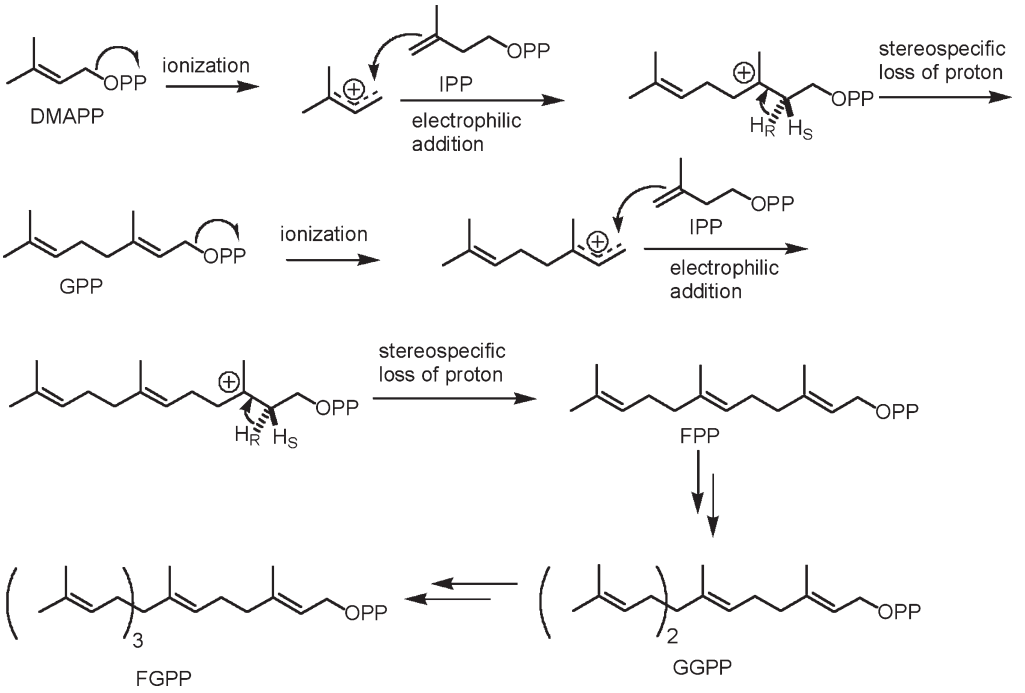

Fig. 2. Biosynthetic pathways of GPP, FPP, GGPP, and FGPP.

3. Pharmaceutical Terpenoids

Terpenoids have a very broad range of biological activities. To review all biologically active terpenoids would be a difficult task, owing to space constraints. In this review we will focus on terpenoids with activities against cancer, malaria, inflammation, and a variety of infectious diseases (viral and bacterial). Other chemotherapeutic agents for these diseases have been the subject of many excellent reviews *(34–71)*. Here, we discuss terpenoids with therapeutic and pharmaceutical functions against these diseases.

3.1. Monoterpenes

Monoterpenes are best known as constituents of the essential oils, floral scents, and the defensive resins of aromatic plants *(72,73)*. Many monoterpenes are nonnutritive dietary components found in the essential oils of citrus fruits, cherry, mint, and herbs. The formation of various monoterpenes from geranyl diphosphate is catalyzed by different terpene cyclases. The general properties of monoterpenes have been discussed in several reviews *(32,74–76)*. A number of dietary monoterpenes have antitumor activity, exhibiting not only the ability to prevent the formation or progression of cancer, but the ability to regress existing malignant tumors *(77)*.

Limonene (**Fig. 3**) is the most abundant monocyclic monoterpene found in nature, and it occurs in a variety of trees and herbs (e.g., *Mentha* spp.). It is a major constituent of peel oil from oranges, citrus, and lemons, and the essential oil of caraway. It has the same skeleton as found in a wide range of important flavor and medicinal compounds,

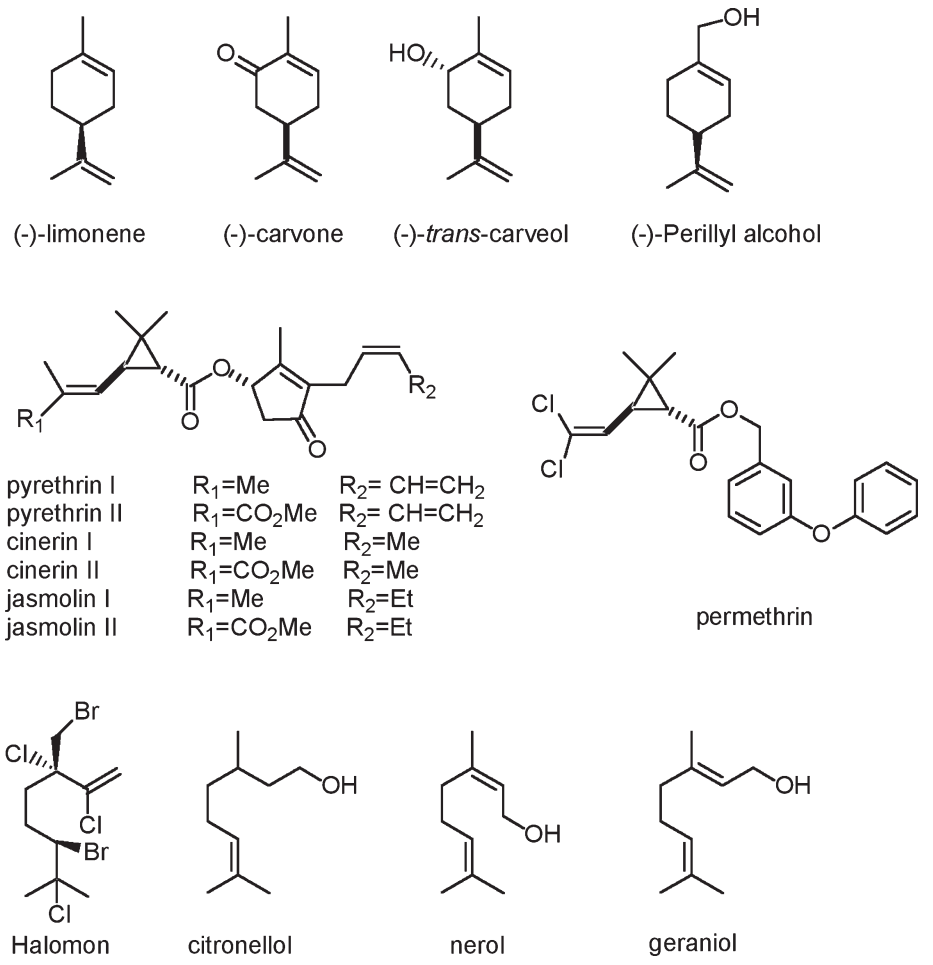

Fig. 3. Monoterpenes.

and consequently, limonene has been an interesting target molecule for chemists and biologists *(78)*. Limonene is a well-established chemopreventive and therapeutic agent against many tumor cells *(65,77,79)*. Carvone, a major monoterpene in caraway seed oil, has been shown to prevent chemically induced lung and forestomach carcinoma development *(80)*. In addition, carveol has chemopreventive activity against rat mammary cancer during the initiation phase *(81)*. Perillyl alcohol, a hydroxylated analog of limonene, exhibits chemopreventive activity against chemically induced liver cancer in rats *(82)* and tumor recurrences in animals *(83)*. Furthermore, perillyl alcohol exhibits chemotherapeutic activity against rat mammary tumors *(83)* and transplanted pancreatic cancer in hamster, with a significant portion of treated tumors being completely regressed *(84)*. Clinical trial testing of chemotherapeutic activity of limonene and perillyl alcohol is in phase I *(85)* and phase II *(86,87)*, respectively. The mechanism of action of monoterpenes against tumor cells is the induction of apoptosis and interference of the protein prenylation of key regulatory proteins *(77,79,88,89)*.

The pyrethrins represent a group of six closely related monoterpene esters and are valuable insecticidal components isolated from pyrethrum flowers, *Chrysanthemum cinerariaefolium*, and several other species in the Asteraceae family *(90,91)*. Pyrethrins are used for treatment of skin parasites such as head lice. They block sodium-channel repolarization of the arthropod neuron, leading to paralysis and death of parasites *(43,92)*. However, minor side effects such as dry and scaly patches, edema, pruritus, and erythema have been reported when pyrethrins are applied in some forms *(92)*. Permethrin, a synthetic analog of pyrethrin, is also used to treat head lice infestation. However, the emerging resistance to pyrethrin and permethrin in head lice has become a serious concern *(93)*.

Among other halogenated acyclic monoterpenes, halomin, isolated from the red alga *Portieria hornemnnii (94)*, is very effective against renal, brain, colon, and non-small cell lung cancer cell lines through a unique mode of action *(95)*. However, further elucidation of its atypical biological activity has been hampered by the limited availability of its natural source, *P. hornemnnii (96)*. Finally, several acyclic monoterpenes—citronellol, nerol, and geraniol—exhibit some activity against *Mycobacterium tuberculosis* with MIC (minimal inhibition concentration) values of 64, 128, and 64 µg/mL, respectively *(97)*.

3.2. Sesquiterpenes

In general, sesquiterpenes are less volatile than monoterpenes. Among the sesquiterpenes, the sesquiterpene lactones are widely distributed in marine and terrestrial organisms and are well known for their wide variety of biological activities *(98,99)*. The anti-inflammatory activities of some medicinal plants result from the presence of one or more sesquiterpene lactones. Feverfew has been used for at least two millennia for the treatment of fever, headaches, menstrual difficulties, and stomach aches *(100)*. Today it is widely used for the relief of arthritis, migraine, asthma, and psoriasis *(101–105)*. Parthenolide (**Fig. 4**), a sesquiterpene lactone, is responsible for the majority of the medicinal properties of this traditional herbal remedy. This sesquiterpene lactone can be found in several species (e.g., *Tanacetum parthenium*, *C. parthenium*, *Leucanthemum parthenium*, and *Pyrethrum parthenium*).

Artemisinin, another sesquiterpene lactone, contains a rare endoperoxide bridge that is essential for its antimalarial activity *(106)*. Artemisinin is derived from an ancient Chinese herbal remedy and has been isolated from *Artemisia annua* (sweet wormwood or "Qinghao"), a species of the Asteraceae family. This herbal plant has been used in Chinese herbal medicine for over 200 years. Artemisinin and its derivatives represent a very important new class of antimalarial drugs, and are used throughout the world. It is effective against both drug-resistant and cerebral malaria-causing strains of *Plasmodium falciparum*. As an antimalarial agent, artemisinin has been extensively reviewed by several researchers *(35,39,56,107,108)*. Chamazulene, α-Bisabolol, and bisabiolol oxides A and B, are terpenoids isolated from matricaria flowers (*Matricaria chamolilla*) and are commonly used in herbal medicine for the treatment of skin inflammation, and as antibacterial and antifungal agents *(13)*. Chamazulene's anti-inflammatory activity is a result of blocking of leukotriene biosynthesis *(109)*.

Many plant sesquiterpenes have also been shown to be effective against the causal agent of tuberculosis (TB), *M. tuberculosis*, which infects approx 8 million people and

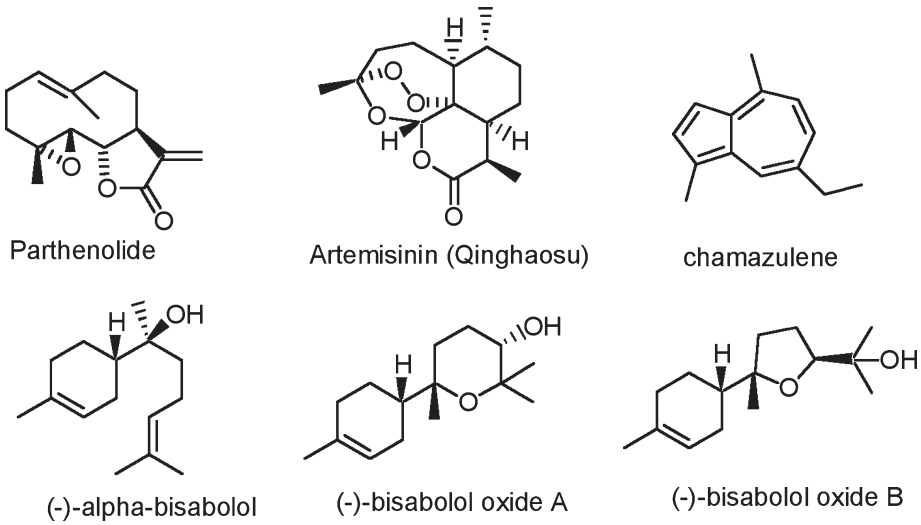

Fig. 4. Sesquiterpenes I.

causes 2 million deaths each year. Tuberculosis is still the leading killer among all infectious disease, especially in developing countries. With the emergence of multidrug-resistant strains of *M. tuberculosis*, the search for new antituberculosis agents has become increasingly important *(48)*. More than 50 sesquiterpenes from plants exhibit significant antituberculosis activity. Sesquiterpene lactones of the germacranolide (**Fig. 5**), guaianolide, and eudesmanolide types are shown to have antituberculosis activity, with MICs ranging from 2 µg/mL to >128 µg/mL. Details of the antituberculosis activity of these sesquiteperne lactones are discussed thoroughly by Cantrell et al. *(45)*.

Many sesquiterpenes isolated from the marine environment also show activity against tuberculosis *(50)*. Axisonitrile-3 (**Fig. 6**), a cyanosesquiterpene isolated from the sponge *Acanthella klethra*, is a potent inhibitor of *M. tuberculosis*, with an MIC of 1.56 µg/mL *(110)*. Puupehenone, 15-cyanopuupehenone, and 15-α-cyanopuupehenol, isolated from sponges of the orders Verongida and Dictyoceratida *(111–113)*, are natural sesquiterpene-shikimate-derived metabolites. Some of them have attracted significant attention from several research groups because of their cytotoxic, antimicrobial, and immunomodulatory activities *(113)*. Puupehenone, 15-cyanopuupehenone, and 15-α-cyanopuupehenol demonstrated 99, 90, and 96% inhibition of *M. tuberculosis* (H3Rv) growth, respectively, at MICs of 12.5 µg/mL. It has been shown that the quinine-methide system in ring D of puupehenone is essential for its inhibitory activity *(50)*.

Sesquiterpene quinines and hydroxyl quoinones and their related compounds represent a prominent class of biologically active metabolites *(114)*. Their occurrence seems to be restricted to sponges of the three families Spongiidae, Thorectidae, and Dysideidae of the order Dictyoceratida, to the family Niphatidae of the order Haplosclerida, and to the algal species *Dictyopteris undulata (115)*. Their remarkable biological activities include antibacterial, cytotoxic, anti-inflammatory, anti-human

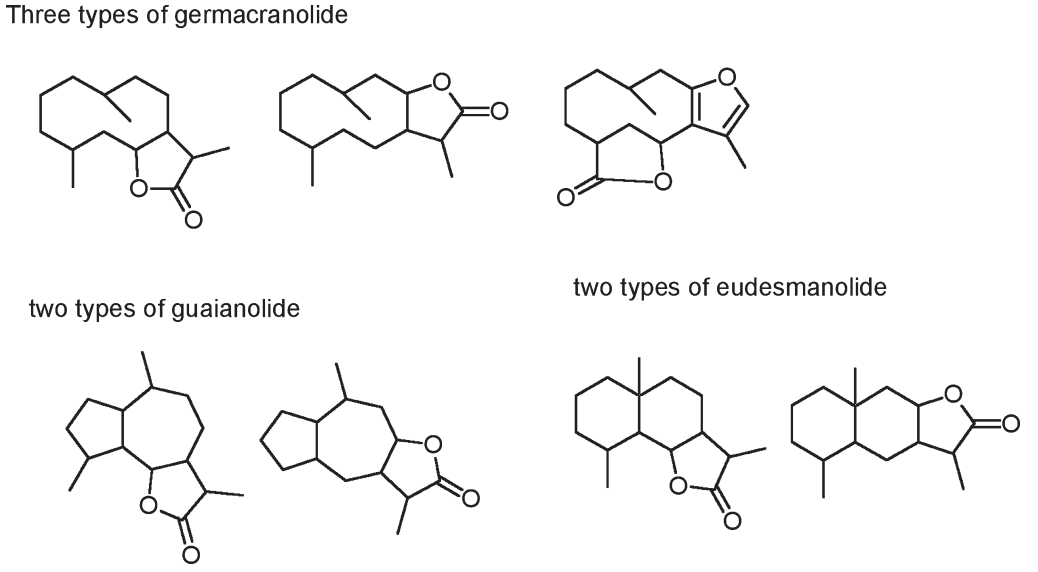

Fig. 5. Sesquiterpenes II.

immunodeficiency virus (HIV), and protein kinase inhibition *(116–120)*. Among these marine sesquiterpenoids, avarol and avarone, isolated from the Red Sea sponge *Dysidea cinerea* have been shown to inhibit HIV reverse transcriptase (RT) with respect to its natural substrate (dNTP) *(121)*. However, their anti-HIV activity was determined in vitro using cell cultures, so it is not yet known whether the anti-HIV activity was a result of inhibition of HIV-1 RT *(48)*. Avarol and avarone also exhibit strong anticancer and antibacterial activities *(122)*. Another quinine sesquiterpene, ilimaquinone, isolated from the Red Sea sponge *Smenospongia* sp., also has been reported to inhibit the RNase activity of the RT from human HIV type I at concentrations of 5–10 µg/mL, while being less potent against RNA-dependent DNA polymerase and DNA-dependent DNA polymerase *(123)*. Ilimaquinone also exhibits antimitotic and anti-inflammatory activities, promotes a reversible vesiculation of the Golgi apparatus, and interferes with intracellular protein trafficking *(124)*. Bolinaquinone, a sesquiterpene hydroxyl quinine, has recently been isolated from the Philippine *Dysidea* sponge *(117)*. It exhibits activity against the human colon tumor cell line HCT116 with an IC_{50} value of 1.9 µg/mL, mild inhibition of *Bacillus subtilis* at 80 µg/disk, remarkable inhibition of phospholipase A2, and anti-inflammatory activity *(117–120)*.

Illudins are a family of natural toxic sesquiterpene compounds with anti-tumor activity, isolated from the basidiomycete *Omphalotus illudens* (*O. olearius* and *Clitocybe illudens*). These compounds are believed to be responsible for the poisoning that occurs when *Omphalutus* is mistaken for an edible mushroom *(125)*. Illudins S and M are extremely cytotoxic and exhibit antitumor activity *(126,127)*. Illudins are effective against various types of tumor cells at picomolar to nanomolar concentrations. A variety of multidrug-resistant tumor cell lines remain sensitive to the illudins *(128)*. Irofulven (hydroxymethylacylfulvene), a derivative of illudin S, has been extensively investigated and is currently in phase II clinical trials. In particular, irofulven exhibits

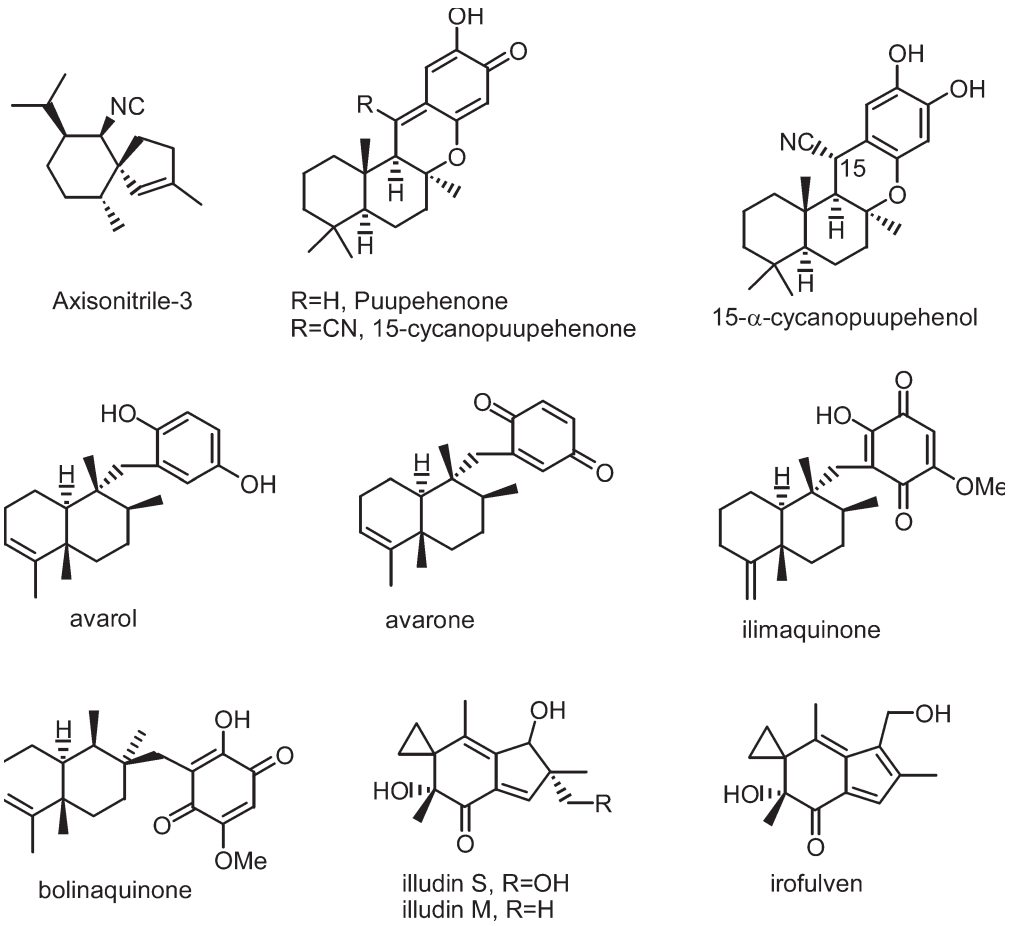

Fig. 6. Sesquiterpenes III.

efficacy against pancreatic carcinoma, a malignancy that is resistant to all other forms of chemotherapy. Irofulven rapidly enters cancer cells, where it binds to cellular macromolecules and inhibits DNA synthesis *(129,130)*. The most unique aspect of irofulven's anticancer activity seems to be its ability to act as a selective inducer of apoptosis in human cancer cell lines, and, in contrast to conventional antitumor agents, this activity of irofulven is effective against tumor cell lines regardless of their p53 or p21 expression *(131,132)*. In addition, the DNA lesion induced by illudins and irofulven is largely ignored by global repair pathways. Therefore, the irofulven and other illudins are considered a new and promising class of tumor-therapeutic agents *(133)*.

3.3. Diterpenes

The diterpenes represent a large group of terpenoids with a wide range of biological activities, isolated from a variety of organisms *(134–146)*. One of the simplest and most important acyclic diterpenes is phytol (**Fig. 7**), a reduced form of geranylgeraniol. This terpenoid is perhaps the most studied biomarker of those found in aquatic environments, and it is a side chain of chlorophyll-a *(12,147)*. (E)-phytol, isolated from

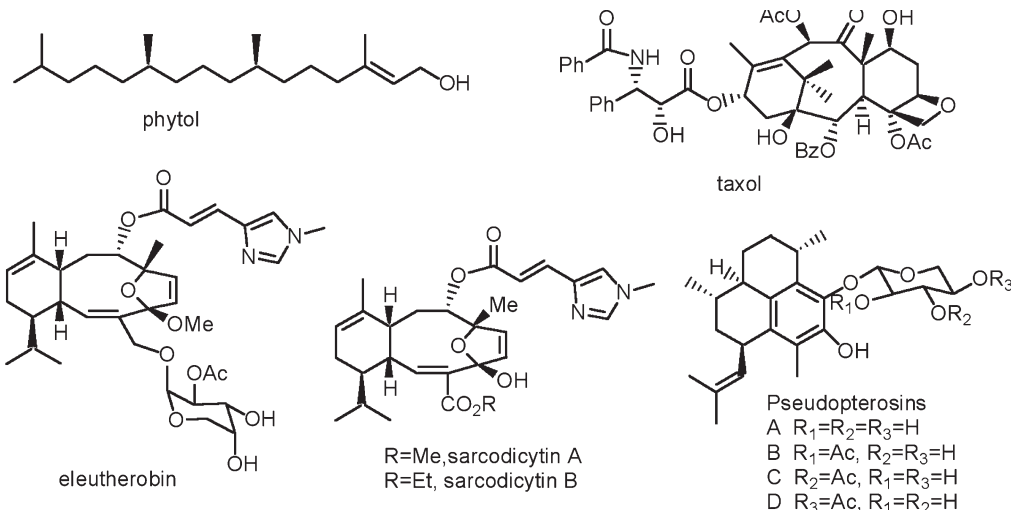

Fig. 7. Diterpene I.

Lucas volkensii, exhibits significant antituberculosis activity, with a MIC of 2 µg/mL *(97)*. Among the cyclic diterpenes, taxines isolated from the common yew (*Taxus baccata*; Taxaceae) represent an important group of compounds whose structure is based on the taxadiene skeleton. Taxines have been well studied because of their anticancer activity *(54)*.

Over 100 different taxanes have been characterized from various *Taxus* species. Paclitaxel (Taxol®) is a member of this group and possesses a four-membered oxetane ring and a complex ester side chain, both of which are essential for anticancer activity. The biosynthesis of Taxol involves complicated cyclizations and modifications (**Fig. 8**). Like epothilones and several other anticancer agents, paclitaxel is able to interact with tubulin (or microtubues) and inhibit cell proliferation by acting on the mitotic spindle through inhibition of microtubule polymerization or microtubule stabilization *(37,38,42,63,148–150)*. Paclitaxel is currently used to treat ovarian, lung, and breast cancers, head and neck carcinoma, and melanoma. It has been hailed as the "perhaps most important addition to the chemotherapeutic armamentarium against cancer over the past several decades"*(151)*.

The development of paclitaxel into an anticancer drug spans several decades. In 1966, a crude extract of bark from the Pacific yew was demonstrated to have a broad range of antitumor activities against several tumor cell lines. In 1971, paclitaxel was identified as the active constituent of the crude extract and its structure determined *(152)*. Paclitaxel was approved by the Food and Drug Administration (FDA) for the treatment of advanced ovarian cancer in 1992 and of breast cancer in 1994. Paclitaxel inhibits microtubule depolymerization, promotes the formation of unusually stable microtubles, and thereby disrupts the dynamic reorganization of the microtubule network required for mitosis and cell proliferation, and causes cellular arrest in the G_2/M phase of the cell cycle *(153,154)*. The protracted arrest of the cell cycle during the mitotic phase is considered to be an important mechanism of paclitaxel-induced cytotoxicity. Nevertheless, the precise mechanisms of cytotoxicity of paclitaxel against

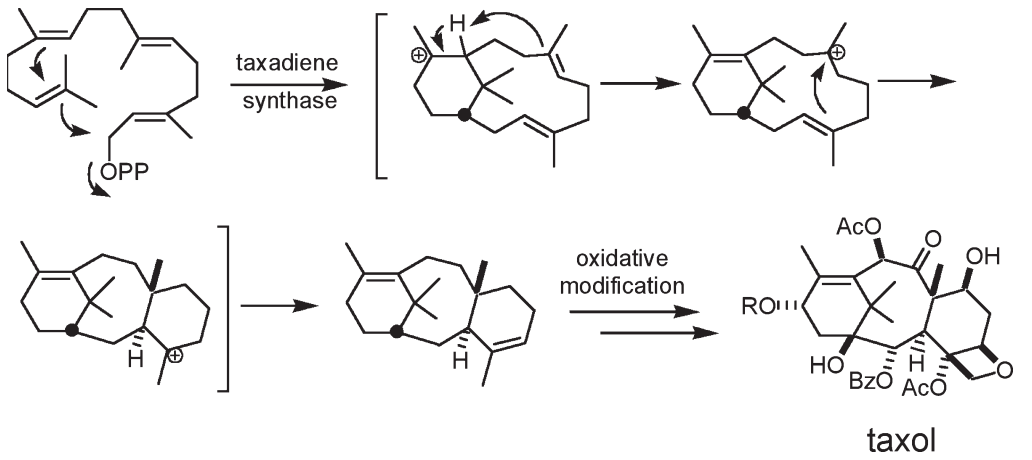

Fig. 8. Biosynthesis of Taxol®.

cancer cells is not entirely clear *(150)*. In addition, the low aqueous solubility and the development of clinical drug resistance are two problems associated with paclitaxel. Furthermore, as for many other anticancer drugs, paclitaxel has several side effects, including neutropenia, peripheral neuropathy, alopecia, and hypersensitivity reactions *(155)*.

Eleutherobin is another microtubule-stabilizing diterpenoid originally isolated from a marine soft coral species of the genus *Eleutherobia (5)*. It was shown to possess activity as an inhibitor of microtubule depolymerization with a mean cytotoxicity greater than those of taxol or the epothilones *(156)*. Eleutherobin belongs to the eleutheside family of marine diterpenoid and is extracted in extremely low yields (0.01–0.02% of the dry weight of the rare alcyonacean *Eleutherobia* sp.). Several elegant total syntheses have been reported *(157–160)*. However, neither chemical syntheses nor the original source have provided sufficient quantities of eleutherobin to permit full in vivo evaluation, and this has thwarted its further development *(161)*. Recently, *Erythropodium caribaeorum*, a relatively abundant Caribbean gorgonian, has been found to be a good source of eleuthesides *(162,163)* and can provide sufficient eleutherobin for preliminary animal studies and chemical transformation to new analogs *(164)*. Sarcodictyin A and B, analogs of eleutherobin, are marine diterpenoids isolated from the Mediterranean stoloniferan *S. roseum (6,7)* and then from the South African soft coral *E. aurea* along with two glycosylated congeners, eleuthosides A and B *(165)*. Sarcodictyin A and B demonstrated very low resistance factors against the P-glycoprotein-overexpressing human cancer cell line *(166)*, and their intrinsic antiproliferative activity against drug-sensitive cells seems significantly lower than those of eleutherobin and Taxol assayed in vitro *(38)*.

Studies involving combinatorial libraries and natural analogs of eleutherobin indicate that the loss of the sugar moiety dramatically changes the potency of eleutherobin against cancer, whereas modification of C-8 side chain has little effect on its potency *(167,168)*. However, the C-8 side chain is essential for the cytotoxicity of the sarcodyctyins; and both imidazole nitrogens are also required *(160)*.

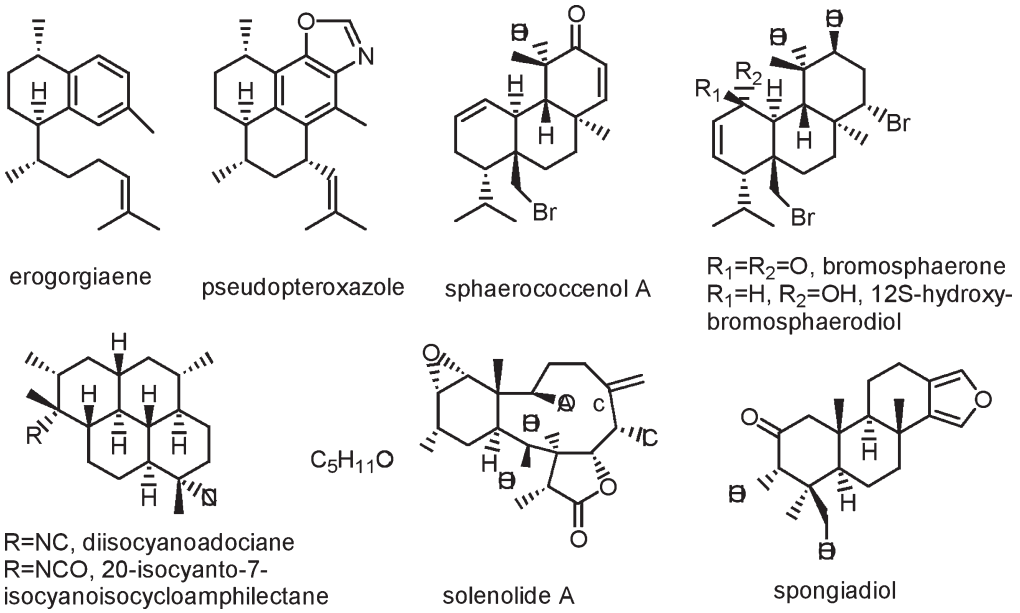

Fig. 9. Diterpene II.

Extracts of the Gorgonian *Pseudopterogorgia elisabethae* show anti-inflammatory activity and are currently used as an ingredient in cosmetic skin-care products *(70)*. The active constituents in the extracts have been identified as diterpene glycosidesm (pseudopterosins), which have analgestic properties and are used for promoting wound healing and as inhibitors of PLA_2 *(169,170)*. Methopterosin (OAS100), a semisynthetic product of pseudopterosin, also has anti-inflammatory activity and is in clinical development for the promotion of wound healing *(55,70)*. Erogorgiaene (**Fig. 9**), a serrulatane diterpene (also known as biflorane), isolated from the West Indian gorgonian *P. elisabethae*, induces 96% growth inhibition for *M. tuberculosis* H37V at a concentration of 12.5 µg/mL *(171)*. The benzoxazole diterpene alkaloid pseudopteroxazole, isolated from the same gorgonian, shows 97% growth inhibition for *M. tuberculosis* H37Rv at a concentration of 12.5 µg/mL without substantial toxic effects *(172)*.

The bromoditerpene sphaerococcenol A, isolated from the red alga *Sphaerococcus coronopifolius* collected along the Atlantic coast of Morocco, has antimalarial activity against the chloroquine-resistant *Plasmodium falsciparum* FCB1 strain, with an IC_{50} of 1 µ*M (173)*. Two other bromoditerpenes, bromosphaerone and 12S-hydroxy-bromosphaerodiol, isolated from the same species, show strong antibacterial activity against *Staphylococcus aureus*, with MICs of 0.104 and 0.146 µ*M*, respectively *(173,174)*.

Diisocyanoadociane, a tetracyclic diterpene with an isocycloamphilectane skeleton, isolated from the sponge *Cymbastela hooperi*, has been reported to have significant antimalarial activity in vitro against two clones of the malaria parasite *P. falciparum (175)*. The tetracyclic diterpene demonstrated significant antiplasmodial activity, with IC_{50} values of 4.7 ng/mL and 4.3 ng/mL and selectivity indices (SI) 1000 and 1100

against the two clones of *P. falciparum*. Another tricyclic diterpene, 20-isocyanto-7-isocyanoisocycloamphilectane, isolated from the same sponge, also shows the same level of antiplasmodial activity and selectivity. In addition, the potency and selectivity of the two tetracyclic diterpenes from the sponge *C. hooperi* rivals the in vitro results obtained with the currently prescribed antimalarial drugs (Artemisinin and chloroquine) *(173)*.

Finally, solenolide A, a diterpene lactone, isolated from a new Indopacific gorgonian species of the genus *Solenopodium*, has been reported to inhibit rhinovirus with an IC_{50} value of 0.39 µg/mL. This diterpene also shows inhibitory activity against poliovirus III, herpesvirus, and the Ann Arbor and Maryland viruses *(176)*. Spongiadiol, a tetracyclic furanoditerpene isolated from deep-water *Spongia* sp., shows inhibitory activity against HSV1 at a concentration of 0.5 µg/disk *(177,178)*.

3.4. Sesterterpenes

Sesterterpenes are the least common group of terpenoids. They are primarily isolated from fungi and marine organisms, and encompass relatively few structural types *(12,13)*. Although many examples of natural sesterterpenes are known, studies of their biosynthesis are rare *(12)*.

Many sesterterpenes inhibit the activity of the human secreted type IIA phospholipase A_2 (PLA_2). LPA_2 is involved in the pathogenesis of a variety of inflammatory diseases via the production of arachidonic acid, the precursor of prostaglandins and leukotrienes. Therefore, secreted PLA_2 has been considered to be a primary target for the development of anti-inflammatory drugs *(119)*. The well-known PLA_2 inhibitors among sponge sesterterpenes are the scalaranes, which were named after scalaradial (**Fig. 10**), isolated from *Cacospongia mollior (179,180)*. Marine sesterterpenes containing the γ-hydroxybutenolide moiety have been studied for their potent anti-inflammatory activity. Manoalide, which is the first marine PLA_2 inhibitor of sesterterpene and a reference compound for this class of natural products, is a potent analgesic and anti-inflammatory agent isolated from the pacific sponge *Luffariella variabilis (181)*. The anti-inflammatory activity of manoalide is ascribed to its irreversible inhibition of PLA_2 *(181–183)*, resulting in inhibition of the formation of pro-inflammatory mediators such as leukotrienes and prostaglandins *(184,185)*. This compound was formerly in phase I clinical trials, but its development was later discontinued *(55)*. Thereafter, many other related molecules have been isolated, such as seco-manoalide, luffariellolide, luffariellins, luffolide, the cacospongionolides, and the petrosaspongiolides M-R *(181,186–192)*, all of which are irreversible inhibitors of PLA_2. Among these compounds, petrosaspongiolide M has been investigated for its pharmacological activity in vivo and in vitro. This compound has significant inhibitory activity against PLA_2 (IC_{50} of 0.6 µ*M*) *(186)* and reduces the level of prostaglandin E2, tumor necrosis factor α, and leucotriene B4 in a dose-dependent manner *(193–195)*. Moreover, it has no significant side effects. Consequently, there is considerable interest in the development of this molecule and its analogs for the treatment of acute and/or chronic inflammation *(194,196)*.

The novel sesterterpene salmahyrtisol A (**Fig. 11**) and three other new scalaranes-type sesterterpenes (3-acetyl sesterstatin 1, 19-acetyl sesterstatin 3, and salmahyrtisol) isolated from the Red Sea sponge *Hyrtios erecta*, show significant cytotoxicity

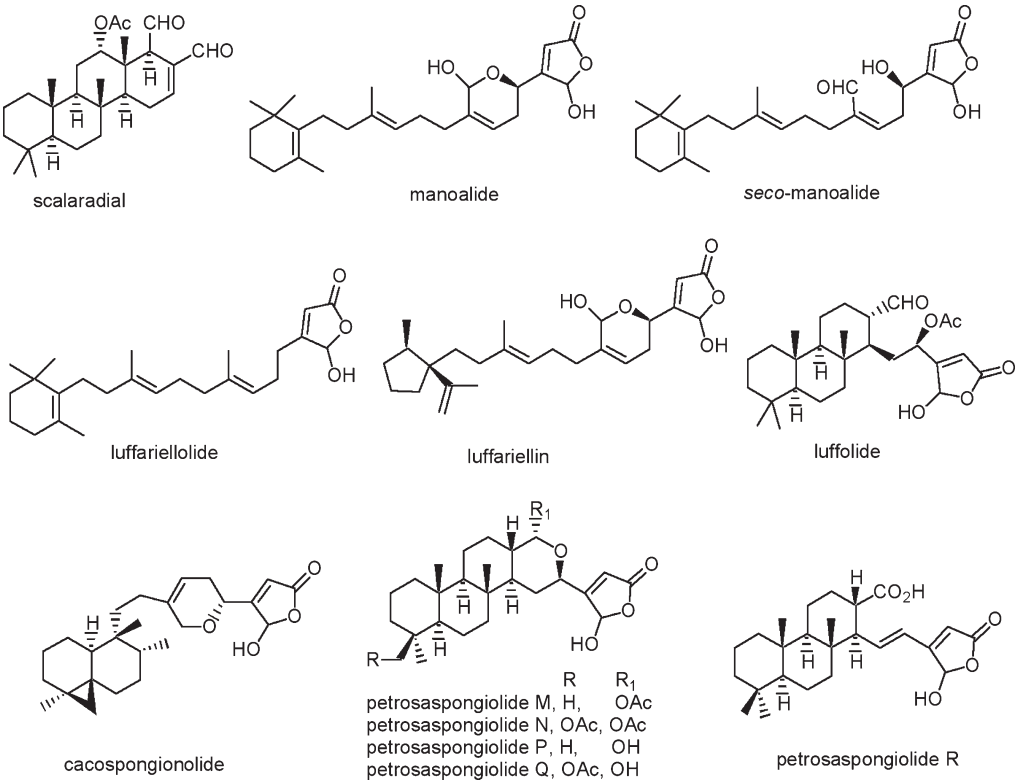

Fig. 10. Sesterterpene I.

against murine leukemia, human lung carcinoma, and human colon carcinoma *(197)*. Halorosellinic acid, an ophiobolane sesterterpene isolated from the marine fungus *Halorosellinia oceanica*, exhibits antimalarial activity, with an IC_{50} of 13 µg/mL, and weak antimycobacterial activity, with a MIC of 200 µg/mL *(198)*. Mangicols A-G are a group of sesterterpenes possessing novel spirotricyclic natural compounds, isolated from the marine fungus tentatively identified as *Fusarium heterosporum (199)*. Among these compounds, mangicols A and B show significant anti-inflammatory activity in phorbol myristate acetate-induced mouse ear edema assay.

4. Chemical Synthesis in Terpenoid Drug Production and Development

During the first part of the 20th century, total synthesis played a central role in identification and structure confirmation of the active principle in a crude extract from natural sources *(200,201)*. However, with the development of modern analytical and purification techniques and spectroscopic methods, structures of most natural products can now be determined unambiguously. Nevertheless, total synthesis is still the ultimate proof for the structure of complex natural products, especially the absolute stereochemistry or remote relative stereochemistry. Many terpenoids with promising biological activity are structurally too complex to be readily synthesized in a cost-effective way via total synthesis from commercially available materials. Semisynthesis,

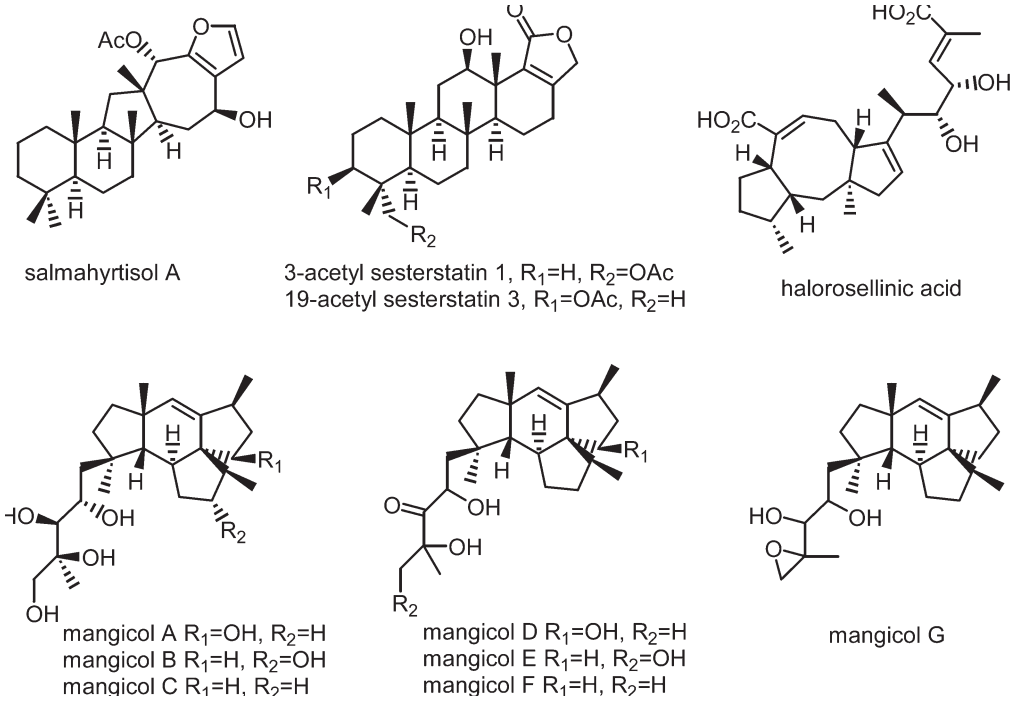

Fig. 11. Sesterterpene II.

on the other hand, has played a major role in the development and production of terpenoid-derived drugs.

The isolation of paclitaxel from nature did not produce enough material for clinical trials *(202)*. In addition, killing yew trees for compound isolation was a big environmental concern. The four-step semisynthesis (**Fig. 12**) of paclitaxel from10-deacetylbaccatin III greatly facilitated the development of Taxol. 10-deacetylbaccatin III was found in the needles of the common European yew tree *T. beccata* as well as a yew tree species found in India. By harvesting and extracting the needles, baccatin III or 10-deactyl baccatin III can be provided in large quantities as precursors of paclitaxel without substantially injuring the tree populations. In addition to paclitaxel, analogs such as docetaxel (Taxotere®) were synthesized in sufficient yield by semisynthesis. Compared with paclitaxel, semisynthetic docetaxel has improved water solubility and is being used clinically against breast and ovarian cancer *(151)*. Six groups completed total synthesis of paclitaxel between 1994 and 2002 *(203–216)*. However, none of their methods are comparable to semi-synthesis in terms of the cost for large-scale production.

Artemisinin (Qinghaosu) has also been produced by semisynthesis. Some phenotypes of *A. annula* have been found to produce as much as 1% Artemisinin, but the yield is normally very much less, typically 0.05–0.2%. The more abundant sesquiterpene in the plant is artemisinic acid (qinghao acid, typically 0.2–0.8%). Fortunately, artemisinic acid can be converted chemically into Artemisinin by a relatively simple

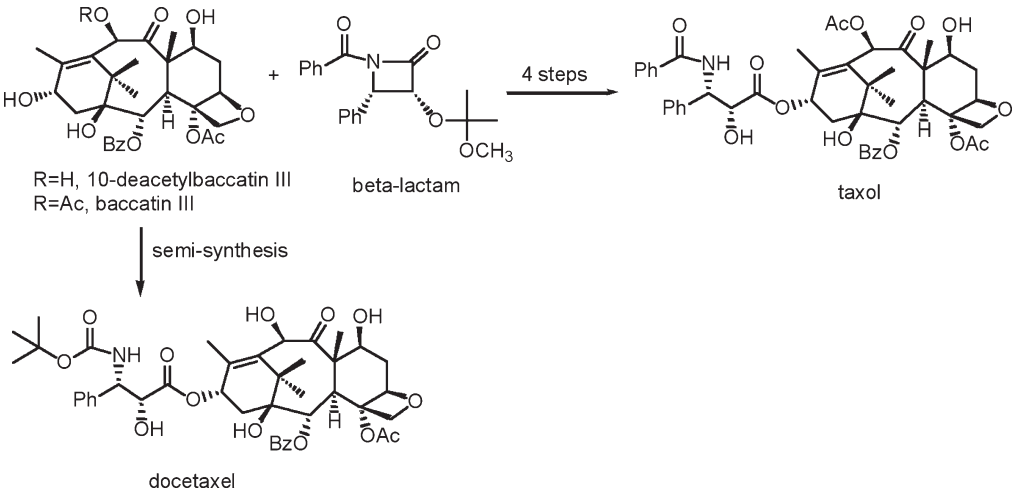

Fig. 12. Semisynthesis of Taxol and its analog.

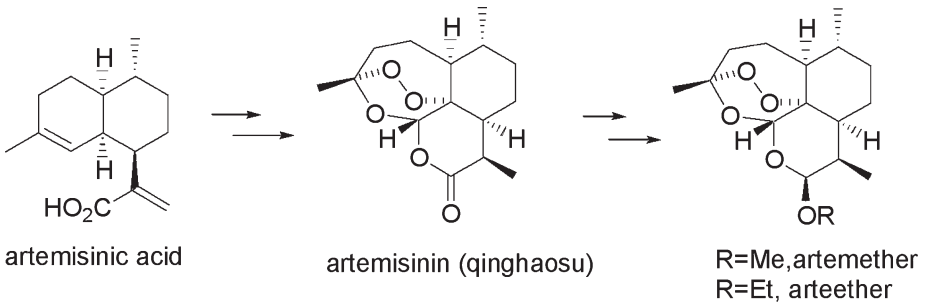

Fig. 13. Semisynthesis of Artemisinin and its analogs.

and efficient process (**Fig. 13**) *(217–219)*. At the same time, Artemisinin can be reduced to the lactol (hemiacetal), and this can be used for the semi-synthesis of a range of analogs, of which artemether, arteether, and the water-soluble sodium salts of artelinic acid and artesunic acid are promising second-generation antimalarial drugs *(220)*. The total synthesis of Artemisinin was completed in 1983, and the peroxy bridge was confirmed to be its unique feature conferring antimalarial activity *(221)*.

Although total synthesis plays a less important role in production of terpenoid drugs, it has been shown to be an important tool in the development of compounds derived from terpenoids and other natural compounds. First, total synthesis is an essential tool for studying structure–activity relationships (SAR). For example, the binding of manoalide to PLA_2 was demonstrated by using the two-masked aldehyde present in the molecule. Extensive SAR studies using chemical synthesis of various analogs have revealed that the minimum structural requirement for activity is the presence in the inhibitor of functional groups able to bind to the amino groups of PLA_2 lysine residues. Many manoalide analogs have thus been synthesized, and many of them share PLA_2 inhibitory properties *(222)*. A similar approach has also revealed

the active moieties of paclitaxel, eleutherobin, sarcodictyin A, and Artemisinin *(106,160,163, 167,168,223)*.

Second, it is often difficult to correlate the relative stereochemistry of remote chiral centers by spectroscopic methods. Total synthesis is the ultimate tool for solving this problem. For example, the chemical structure of eleutherobin was elucidated by extensive two-dimensional nuclear magnetic resonance spectroscopy and mass spectrometry *(5)*. L-arabinose, the sugar moiety of eleutherobin, appeared to be favored in nature. This was proved to be wrong by total synthesis. The relative stereochemistry of the diterpenoid 4,7-oxaeunicellane skeleton and the arabinose of eleutherobin were assigned by the Danishefsky and Nicolaou groups through total synthesis *(224–227)*. It is remarkable that they could unambiguously identify the sugar unit of eleutherobin as D-arabinose despite the fact that L-arabinose is the natural abundant enantiomer.

Finally, libraries of structurally diverse natural-product-like molecules have contributed to the understanding of biological processes in small molecule-based systematic approaches *(228)*. Efficient access to diversity can be achieved in diversity-oriented synthesis using pairs of complexity-generating reactions, where the product of one is the substrate for another *(229)*. Diversity can also be achieved by chemical modification of natural products. For example, the potential of macrocyclic diterpenoids to afford natural-product-like polycyclic compounds was demonstrated by the conversion of two lathyrane *Euphorbia* factors into a series of densely functionalized diterpenoids of unnatural skeletal type (**Fig. 14**) *(230)*.

5. The Sustainable Production of Terpenoids

Like many other natural products, terpenoids are usually extracted from the source organism in extremely low yields. Producing an adequate and sustainable supply of these compounds has been one of the major challenges for developing terrestrial and marine organism-derived natural terpenoid compounds into clinically useful entities *(164)*. Harvesting source organisms from the environment for the target terpenoid is not a feasible strategy because of environmental and ecological concerns, especially for terpenoids derived from marine environments. For example, eleutherobin, a structurally complex diterpene glycoside, constitutes 0.01–0.02% of the dry weight of the rare alcyonacean coral *Eleutherobin* sp. *(5)*. The limited supply of paclitaxel from its primary source once hampered the development of paclitaxol into a clinically used drug *(150)*. The limited supply of eleutherobin has restricted the evaluation of this promising marine diterpene *(162)*. Consequently, a serious obstacle to the commercial development of most promising terpenoids is their availability from the natural environment. To provide enough material for preclinical evaluation and clinical trials, several approaches have been used to produce terpenoids with promising biological activities, and their implementation should greatly facilitate the development of novel terpenoid-related drugs.

5.1. Metabolic Engineering

The redirection of metabolic pathways for enhanced production of existing natural products or for production of "unnatural" natural products has been an active area of research. Metabolic engineering, which integrates engineering design and systematic and quantitative analysis of pathways using molecular biology, modern analytical tech-

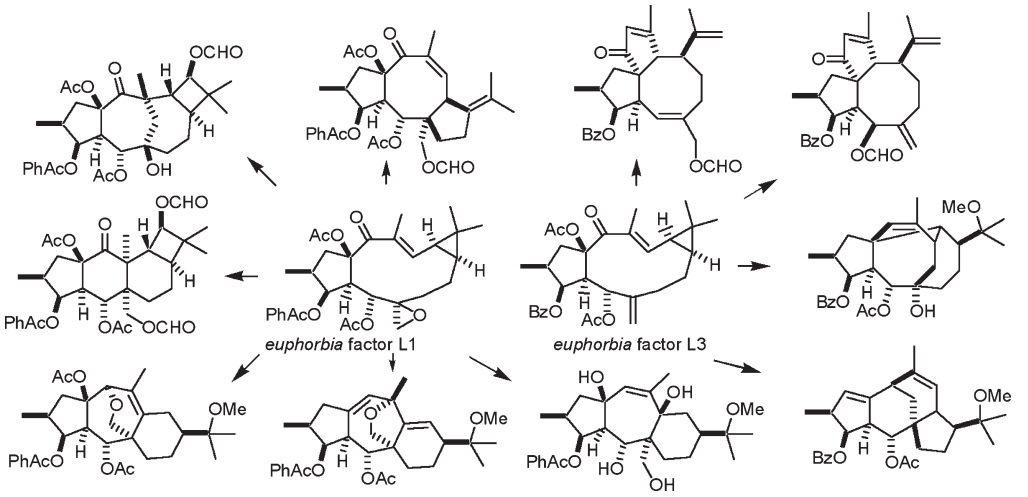

Fig. 14. Diversity via natural-product derivatization.

niques, genomic approaches, and "-omics" technologies into production of natural products, will provide alternative approaches to produce terpenoids with pharmaceutical value. Indeed, enhancing monoterpene yields and changing the metabolite composition of essential oils in plants has been shown to be feasible. Using the transgenic plants to increase the production of monoterpenes for scent and flavor has been demonstrated in flowers *(231,232)* and fruits *(233)*. Moreover, the pathway engineering approach has been used to successfully produce several interesting sesquiterpenes, including amorphadiene, the precursor of the antimalarial drug artemisinin, in *E. coli (234,235)*. As a powerful tool for the production of both natural products and the library of their analogs, the engineered fermentable microbial host will provide renewable and sustainable resources to generate terpenoids with interesting biological activities.

5.2. Cell Culture and Others

Advances in cell culture have also provided a promising means for the production of valuable secondary metabolites from plants. Production of paclitaxel and other taxanes using cell-culture techniques has been well established. The level of taxoid production in bioreactors has been reported to reach 612 mg/L in *T. chinensis* cell cultures *(236)*. Strategies for enhancing paclitaxel and its precursors have been reviewed extensively by Zhong *(237)*. At the same time, the production of artemisinin has also been pursued in callus, cell suspension, and shoot and hairy root cultures of *A. annua (238–242)*. Undifferentiated callus and cell suspension cultures produce extremely low yields of artemisinin. However, differentiated shoot cultures and hairy roots show promising potential for artemisinin production *(237)*. Compared with the paclitaxel production level, the production yield of artemisinin in cell culture is still not significant enough to be used for commercial purposes.

The bioprocess engineering of marine macroalgae for the production of halogenated monoterpenes has been carried out in small-scale tissue-culture bioreactors *(243–245)*. In the established system, the photosynthetic tissue culture was developed for

the marine red algae *Ochtodes secondiramea* and *P. hornemannii* using callus-induction and shoot-regeneration techniques. Rates of monoterpene production have been shown to be affected by temperature, light intensity, and nitrate concentration in the growth medium *(246,247)*. Metabolic flux analysis indicated that the halogenated monoterpene production was not limited by its precursor (myrcene) and that chlorination is the target for increasing the production *(248)*.

Recently, aquaculture systems designed and engineered for the production of large quantities of biomass of two species of marine invertebrates (*Bugula neritina* and *Ecteinascidia turbinate*) have been established in order to harvest their natural chemical constituents *(249)*. Aquaculture will also provide an alternative approach for producing valuable terpenoids from marine invertebrates in a reliable, renewable, and cost-effective way. However, additional research is still needed in order to optimize controlled environment culture systems and to explore the feasibility of such systems for other marine invertebrates. Finally, the Caribbean gorgonian *E. caribaeorum* has been cultured in shallow running seawater tanks located in a greenhouse under ambient sunlight illumination *(164)*. The cultured *E. caribaeorum* produce eleutherobin and the briarane diterpenoids erythrolides A and B in yields comparable to those reported from wild-harvest reef animals. Therefore, the aquaculture could enhance large-scale marine terpenoid production in the near future.

6. Concluding Remarks

Terpenoid-derived drugs have contributed significantly to human disease therapy and prevention. Some terpenoid drugs have provided tremendous benefits for patients and for the pharmaceutical industry. Artemisinin and its derivatives comprise a multimillion-dollar market worldwide. Taxol alone is estimated to have annual sales of over $1.8 billion. Terpenoids indisputably continue to be important compounds for drug discovery. In last two decades in particular, many terpenoids with promising biological activities have been isolated from diverse marine environments. These marine terpenoids exhibit an impressive array of novel structural motifs, many of which are considered to be derived from biosynthetic pathways that are exclusive to marine organisms. Moreover, most of these marine terpenoids possess remarkable biological activities whose potential benefits extend beyond the marine ecosystem and embody the development of new antifungal, anticancer, anti-inflammatory, and antiviral drugs *(250)*. Although marine natural-product bioprospecting has begun only relatively recently, it has already yielded over a thousand novel molecules. Marine natural-compound bioprospecting will continue to provide more promising terpenoids and other natural products for drug development. In addition, marine biodiversity is estimated to be much greater than that on land *(55)*. Many marine animals, plants, fungi, and algae are rich sources of novel terpenoids. With the continuing exploration of the oceans and affordable technology for the exploration of the deep oceans, more novel terpenoids with promising biological activities are expected to be discovered from marine environments in the near future.

In addition, chemical synthesis (e.g., derivatization of natural products) and combinatorial synthesis of natural product analogs can also play a significant role in providing SAR data for a particular target. Accurate knowledge of the structural features required for activity in each compound class will give the predictive power of

pharmacophore models. For example, several pharmacophore models have attempted to reconcile the SAR data for taxoids and other compound types in order to generate a sufficiently detailed understanding of tubulin-binding requirements. Information from this approach will allow rational design of new classes of microtubule-stabilizing drugs. The terpenoids encompass a wealth of significantly diverse compounds, providing chemists with great opportunities to synthesize not only new, valuable terpenoid drugs, but also novel terpenoid compounds that can be used as tools for understanding biochemical pathways.

Finally, along with the information derived from the human genome and metabolic pathways, high-throughput technologies such as proteomics, transcriptomics, and metabolomics will greatly shorten the time required for assaying natural compounds in vivo and in vitro. In parallel, new analytical instruments and synthetic approaches will further facilitate both the identification of terpenoids from natural sources and better understanding the SAR. In particular, marine biodiversity is far beyond what we have dreamed. Isolation and identification of marine terpenoids should draw more attention from drug discovery and development. Engineered new assays and high-throughput tools should facilitate identification and isolation of new terpenoids. There is no doubt that more terpenoid-based clinical drugs will become available and play a more significant role in human disease therapy.

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