Terpenoids Against Human Diseases

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Edited by
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Dedicated to the Next Generation

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Contents

Preface

Terpenoids are a group of metabolites showing much functional diversity in the treatment of human disease. Over the last few decades, a huge volume of work has been reported in the medical literature, but no such book has been published with a complete compilation of all the recent important works in a single volume to date. A book such as *Terpenoids Against Human Disease* is highly required at this stage.

Interestingly, terpenoids have a role in treating some important human diseases—including liver disease, neurodegenerative disease, cancer, infectious diseases, cardiovascular disease, and inflammatory disease—that are addressed in detail in this book. This book is a valuable resource for its classification of terpenoids and their chemical properties and for its logical representation of the metabolic engineering approaches to terpenoid production, the toxicity of terpenoids in living systems, and terpenoid molecules as biological messengers leading to therapeutic efficacy against human disease. Moreover, applications of terpenoids in disease models are noted and thoroughly discussed in reference to *in vitro* studies as well as *in vivo* studies with clinical trials.

This book can be referred to as a knowledge resource for academic institutions and the pharmaceutical industry. In addition, it may be an interesting asset to researchers in the fields of medicinal chemistry, pharmaceutical chemistry, natural products, and remedial biotechnology of pathological disease.

This book is composed of chapters written by multiple authors—including myself—all of whom are experts in their respective fields and ultimately compiled and edited by me. I hope that the readers of this book will become aware of the enormous potential of terpenoids and will try to discover a few novel applications. I also hope this book will serve to stimulate multidisciplinary studies on terpenoids, resulting in an optimal utilization of this "green" chemical in the near future.

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I owe my deepest gratitude to my institute, the National Institute of Technology–Agartala, Tripura, for its academic environment that in all respects enabled me to compile and edit this book on *Terpenoids Against Human Disease*. I am also indebted to Prof. Harish Kumar Sharma, Director, and the administration of the institute for all the support without which it would not have been possible to publish this book in its present form.

A special word of appreciation to all those who contributed chapters to complete this project. They have presented their understanding of the complex relationships between terpenoids and pathological diseases. I would like to express my sincere thanks to them for sharing their precious knowledge of this critical field with the readers.

I would like to mention all of my family members—especially my parents, my wife, and my daughter—they played an important role in the completion of this book with their continuous support, encouragement, appreciation, and inspiration. Without their assistance, I could not have finished this project successfully.

Last, I express my heartiest thanks to the publisher, CRC press (Taylor & Francis Group), for their assistance and cooperation in publishing this book.

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Dijendra Nath Roy, PhD, has been an assistant professor in the Department of Bio Engineering, National Institute of Technology, Agartala, India, since 2013. He received his professional bachelor degrees from the Haldia Institute of Technology, West Bengal University of Technology (BTech, 2005), and his Doctor of Philosophy degree from the CSIR-Indian Institute of Chemical Biology (PhD in Bioengineering, 2011). Dr. Roy carried out postdoctoral research training at the National University of Singapore, Singapore (2011–2012), after which he was appointed to his present position. Dr. Roy is a member of numerous professional bodies including the Indian Science Congress Association, Government of India, and the Institution of Engineers, Kolkata, India. In addition, Dr. Roy has earned several project grants from different external funding agencies in India to carry out research on product development, especially drug development. In 2015, he was honored with the prestigious Young Scientists award from the Science and Engineering Research Board, Department of Science and Technology, Government of India, to implement his research ideas into development in the laboratory. He is pleased to publish this book from CRC Press, Taylor & Francis Group, USA, for those who are actively engaged in drug development.

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1

A Brief History of Terpenoids

**Milena Campelo Freitas de Lima, Larissa Sousa da Silva,
Larissa Silveira Moreira Wiedemann and Valdir F. da Veiga Jr.**

CONTENTS

1.1 Terpenoids: General Overview

Living beings have developed adaptation mechanisms essential for their survival throughout their evolutionary process. In the plant, animal and microorganism species, unique metabolic routes have been developed with the objective of acting in defence and, consequently, they attribute specific characteristics to their species. Substances produced by these routes have been designated as secondary metabolites or, as some authors prefer, special metabolites (Pinto et al. 2002; Simões et al., 1999).

Terpenes are a class of special metabolites, a set of substances capable of acting on behalf of their producing species. The meaning of the term terpene appeared in the nineteenth century, based on studies carried out with the plant *Pistacia terebinthus*, whose resin is termed terebinth or tupertin, a name derived from the German 'Terpentin'. The word terpene was first used by Kékulé in 1866 as a way of generalizing substances from this class (Kung and Yang, 1998; Simões et al., 1999). Subsequently designed as terpenoids (Figure 1.1), the substances from this class have widespread occurrence in the plant, animal and microbial kingdoms. Their distribution is greater in the plant kingdom, where they are generally found in resinous and aromatic plants. They vary in type and quantity between parts of plants such as leaves, bark, twigs, trunk, fruits and seeds. For each part of the plant, the percentage of the composition may vary (da Veiga Jr. and Pinto, 2002; Breitmaier, 2006).

These compounds can also be found in animals, although they are not so common. One of the earliest reports of animal terpenes was in musk oil, obtained from the secretion of the musk deer and beaver. With the abundant use of these oils by the European peoples, these animals began to be in danger of extinction. The advancement of studies in the field of the chemistry of natural products made it possible

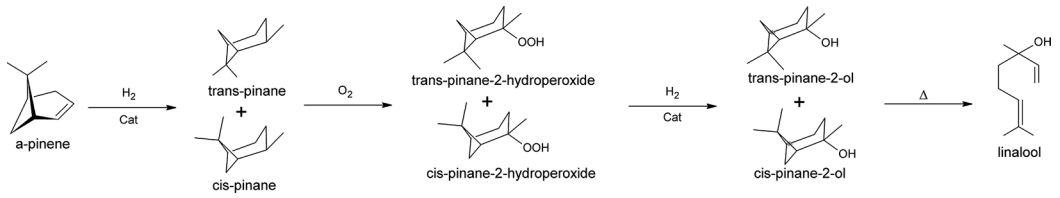


FIGURE 1.1 Scheme of linalool semi-synthesis.

to identify the compounds and synthesise them, thus reducing the use of animals to obtain the active principles of these oils (Dias and Silva, 1996). Other natural sources of terpenes can be found in microorganisms such as fungi and bacteria. Identification in this group was only possible due to the advancement of biotechnology, where the study of the cultivation of these microorganisms can be analysed as to its composition (Chiappini et al., 2008).

Historical accounts show the medicinal use of extracts containing terpenes dating from 1500 to 1000 BC in both traditional Chinese and Ayurvedic medicine and in ancient Egyptian cultures. Over the years, other applications have been attributed to terpenes, such as use as incense in religious rituals and perfumes (Dias and Silva, 1996).

Resin-producing plants are usually rich in terpenoids. The incenses (Burseraceae) and the Amazonian copaiba oils (*Copaifera* sp., *Fabaceae*) are examples of oleoresins whose application has always been related to the treatment of diseases. Currently, terpenoids are used in various industrial sectors such as perfumery, cosmetics, food and drug production (da Veiga Jr. and Pinto, 2002; Bizzo et al., 2009).

The advancement of the studies in the chemistry of natural products allowed discovering the importance of these metabolites. Until the 1960s, several authors suggested that secondary metabolites, especially terpenes, would be the residues of the primary metabolism. What was once thought to be only the excretion of vegetation, today is a source of products with great industrial relevance, encouraging new discoveries about these compounds (Simões et al., 1999).

1.2 Sources

1.2.1 Natural Sources

Since the dawn of time, plants have represented the main natural source of terpenoids. With the control of fire by man, about 400,000 years ago, appeared the first observations of aromatic compounds from the burning of plants. The discovery of fire was an extremely important historical landmark in the discovery of the first aromas, as primitive peoples realized that the burning of some plants produced pleasant aromas. Influenced by the force of religion, philosophical currents and delicious aromas, the production of aromas by the burning of plants became more and more common on primitive man's life.

Incense applied in environment aromatization was the first scents employment, also used as repellents. They began to compose the best places in society and to be part of the life of the most renowned people of the time. With the improvement of the practices of the production of aromas, the aromatic plants began to be used not only in the form of incense, but also by the immersion of their flowers in alcohol, leading to the production of perfumed balms and oils, introducing a technique that today we know as maceration.

The aroma production process from the plants went beyond the maceration, but techniques currently relevant in the international market for essential oils, such as distillation and enfleurage, were introduced many centuries ago. The distillation was developed and improved by the alchemists, around the fourteenth century, in search of explanations on the composition and the transformations

of the matter. The medieval alchemy distillation was used to obtain 'medicinal waters', with several therapeutic purposes (Beltan, 1996).

Contextualizing the discoveries and applications of a series of medicinal waters, and at the same time of improvement of the technique of distillation, the 'quintessence' appears, by product of the distillation of the medicinal waters. In allusion to the fifth Aristotelian element constituent of the heavens, to these aromatic magical waters were attributed and potent healing power properties. In medieval culture, quintessence was considered sacred, of divine origin, reflecting the essence of the vegetable. It was believed that its excellent therapeutic application would be in function of its divine nature and this healing power could be reached by extracting that essence from the materials by distillation (Beltan, 1996).

In this philosophical thought of quintessence was born the term that gave rise to the expression 'essential oil' (Beltan, 1996). Today, we know that essential oils represent the largest natural source of terpenoids. Terpenes with low molecular weight, such as monoterpenes and sesquiterpenes, which are weakly oxygenated, are volatile and responsible for the main organoleptic characteristics of the essential oils, giving them colour, flavour and aroma. About 90% of the chemical composition of the essential oils corresponds to these terpenoids. They are the main compounds responsible for the various applications of essential oils in the cosmetics, pharmaceutical, perfume, and food industries.

1.2.1.1 Monoterpenes

1.2.1.1.1 Alpha and Beta-Pinene

Pinenes are bicyclic hydrocarbons from monoterpene class with wide distribution on Coniferae oil resins. The isomeric mixture of pinenes was first described from the volatile fraction of *Pinus* resin, such as terebinth or turpentine, being called australen (mainly D-pinene, from American *Pinus australis*) or terebentene (French oil resin, chiefly L-pinene). Observed in several other oil resins, the pinene isomeric mixture received many other designations, such as oliben, from *Olibanum* species (Heusler, 1902). Pinene designation was assigned by Wallach, around the 1800s, sealing forever its relationship with the botanical family where pinenes are more abundant, *Pinaceae* (Bradfield et al., 1932). Terebinth is one of the oldest oil resins in human history. Its use as a solvent has appeared in the literature since the thirteenth century. The first terebinth was obtained from the pantropical *Anacadiaceae pistaceae terebinthus* (Bradfield et al., 1932).

The huge commercial interest in terebinth is intrinsically related with the pinene concentration, the main compound from the volatile fraction, which comprises 75%–90% of the oil. Pinenes are applied in cosmetic and food industries, as flavour and coadjuvants in several formulations. They are also used as precursors to important industrial synthetic resins and aromatic substances, such as α-terpineol, verbenol, linalool and others (Vespermann et al., 2017).

Pine tree is presently the major natural source of pinenes, a highly profitable vegetal species, with fast growing, easy adaptation, commercial demand to several of its products, from oil resin to the trunk, and highly accepted by international markets (Rodriguez et al., 1976). The oil resin extraction from pine tree was the only way to obtain terebinth for several years. Recently, another process route was developed as a by-product of the paper and cellulose process industry (Sell, 2003). Terebinth sulphate is a by-product when wood pulp is chemically produced from conifer, pine and other coniferous trees using the Kraft process.

1.2.1.1.2 Linalool and the Rosewood Essential Oil

The history of essential oils goes back to the alchemists, and especially Mary, the Jewess, who would have been one of the inventors of the processes of dragging the lighter substances of the plants using the boiling water, a process that became known as the steam water or steam distillation. The essential oils industry had its first major breakthrough in the early twentieth century, with the development of distilleries suitable for extraction on a larger scale.

Around 1921, rosewood essential oil (*Aniba rosaeodora* Aublet, Lauraceae) entered the international market, being quickly added in the formulation of a new famous French perfume, Chanel #5, that would

be very successful (Ereno, 2005). From its discovery to the present day, this species has gone through a long process of adaptation and progress. Several botanical classifications were attributed to this species. It was discovered in 1762, in the Amazonian region of French Guiana. Indigenous people from that region call it 'licaria'. Aublet, its discoverer, initially classified it as *Licaria guianensis* Aublet (Leite et al., 1999; Marques, 2001). The first essential oil of this species was extracted from the wood of the tree trunk, in 1875, by Samarin (Leite et al., 1999). Excessive exploitation of this species has propelled oil-producing companies to seek new populations of rosewood, entering the Brazilian Amazon, more and more to the west. They settled in Amapá, in 1925, in Pará and then in Amazonas, Amazonian Brazilian states (Ferraz et al., 2009). Nowadays, we know that the essential oils of this species can be obtained from different parts of both the trunks and the branches and leaves (Ereno, 2005). The incessant predatory extraction of rosewood in search of its essential oil contributed to the scarcity of this species. Its main constituent is the linalool. This monoterpene, a volatile terpene of only 10 carbons, is present in a few plant species. The high interest for the essential oils of this species is related both to the concentration of linalool and to its stereochemistry. Only the (*R*)-linalool enantiomer, present in rosewood, is responsible for the strong aroma and fixation properties of these oils (Bizzo et al., 2009). Other natural sources of linalool, such as *Cinnamomum camphora*, have arisen to supply the demand for this much-desired monoterpene. With the emergence of synthetic linalool, there was an appreciable decrease in the production of the essential oils of Aniba rosaeodora, contributing directly to the preservation of the species (Coppen, 1995). With the mismanagement of rosewood trees, its use was restricted to fine chemicals (Homma, 2003). Although this species was naturally occurring and widely distributed in the Guianas and Amazonian countries, with the intense exploitation of the rosewood, Brazil is currently the only supplier of the essential oil of this species in the world, with export port only in Manaus, Amazonas. The world production of natural linalool is therefore concentrated in a single region (May and Barata, 2003; Bizzo et al., 2009).

1.2.1.1.3 Limonene

Limonene, another commercially relevant terpenoid, is a hydrocarbon monocyclic monoterpene that is amongst the most abundant substances in nature. It can be found in both the racemic and the enantiomeric forms. D-Limonene is the most common enantiomer, it can be found in the essential oils of the pericarp of many citrus fruits such as oranges, mandarins and lemons, corresponding to 95% of the chemical composition. L-Limonene is less recurrent in nature and can be found in small concentrations in the plant species of *Mentha* spp. and some conifers such as *Abies alba* (Heusler, 1902).

From its discovery in 1854 to the present day, industrial use of D-limonene underwent an extensive use process. Its commercial expansion, by Henry Schulz, began in 1950, in Florida. This enantiomer was marketed as an alternative to non-toxic solvents and combined with surfactants in the formulations of various cleaning products. Subsequently, as an insecticide, it was the first natural substance used in the control of biological pests. The insecticides that contain D-limonene are used as insect repellents in the control of fleas in pets and mosquito larvicides (Ciriminna et al., 2014). With the green chemistry approach, the use of limonene, obtained from waste material, as an industrial solvent has become more and more important.

1.2.1.2 Diterpenes

Diterpenes are common compounds naturally exuded from the trunks of the Cistaceae, Leguminoseae, Burseraceae, Lamiaceae and Euphorbiaceae botanical families as an adhesive lipophilic resin (Bhat et al., 2005). They are responsible for the high viscosity and density from natural gums and oil resins in a wide variety of diterpenic skeletons including labdane, pimarane, abietane, kaurane, clerodane and giberellane (Breitmaier, 2006).

Some important representative substances from these oil resins are pimarane and the abietane derivatives, pimaric and abietic acids, commonly found in terebinthin oil resins (Sell, 2003); glycolyzed diterpenes, such as steveoside and ribaudiosides, from the leaves from Stevia rebaudiana (Geuns, 2003;

Gupta et al., 2016); and labdane, clerodane and the kaurene medicinal acids copalic, hardwickiic and kaurenoic from the *Copaifera* genus (Veiga Junior and Pinto, 2002), the last one, a gibberellin derivative.

The leaves from *Stevia rebaudiana* Bertoni represent the main natural source of glycolyzed diterpenes. About 30 steviol derivatives were described for this species, rebaudioside A and stevioside are the main substances, the last one in about 20% of the dry leaves of *Stevia* (Gupta et al., 2016).

Stevia rebaudiana (Asteraceae) is a perennial shrub native to South America, known worldwide for its sweet leaves. The first studies with this plant were performed by Moisés Santiago Bertoni in Paraguay, in 1887, and it is called by the local Tupis-guaranis indigenous people 'Yerba de Paraguay' or 'Yerba Dulce' and is used as a natural sweetener (Filho, 2003). Stevioside was first isolated in the early 1900s, mixed with other glycolyzed diterpenes. Together with rebaudioside A, they represent an enormous potential substitute for sucrose—because of the intense taste a non-caloric way—as an alternative sweetener to people with diabetes, phenylketonuria and obesity (Geuns, 2003; Gupta et al., 2016).

*1.2.1.2.1 Diterpenes of Copaiba (*Copaifera *sp.)*

Oil resins from *Copaifera* genus (Leguminoseae) are between the oldest natural sources of diterpenic acids. Since the very first Jesuit priests initiated contact with the Brazilian indigenous people in the early 1500s, the magical curative properties of the oil resin began to be written about in chronicles that crossed the Atlantic Ocean. About three centuries after the first descriptions of the properties, the oil resin was fractionated by Theodore Peckolt in Brazil, and by the 1900s, by German scientists, who were describing its homocopalic acid characteristics. Soon, several other labdane resinous acids were isolates and their chemical structures identified, together with clerodanes and kauranes (Figure 1.2). Recently, the diterpene composition of the so-called copaiba oils was reviewed and more than 40 different diterpenes were described (Veiga-Junior and Pinto, 2002; Leandro et al., 2012).

The labdane skeleton is one of the first diterpenes formed by biosynthesis. The name has its origin in a Mediterranean oil resin called labdanum, exuded from the trunk of the *Cistus labdaniferus* tree species, the first resin from which this type of diterpene was concentrated (Breitmaier, 2006).

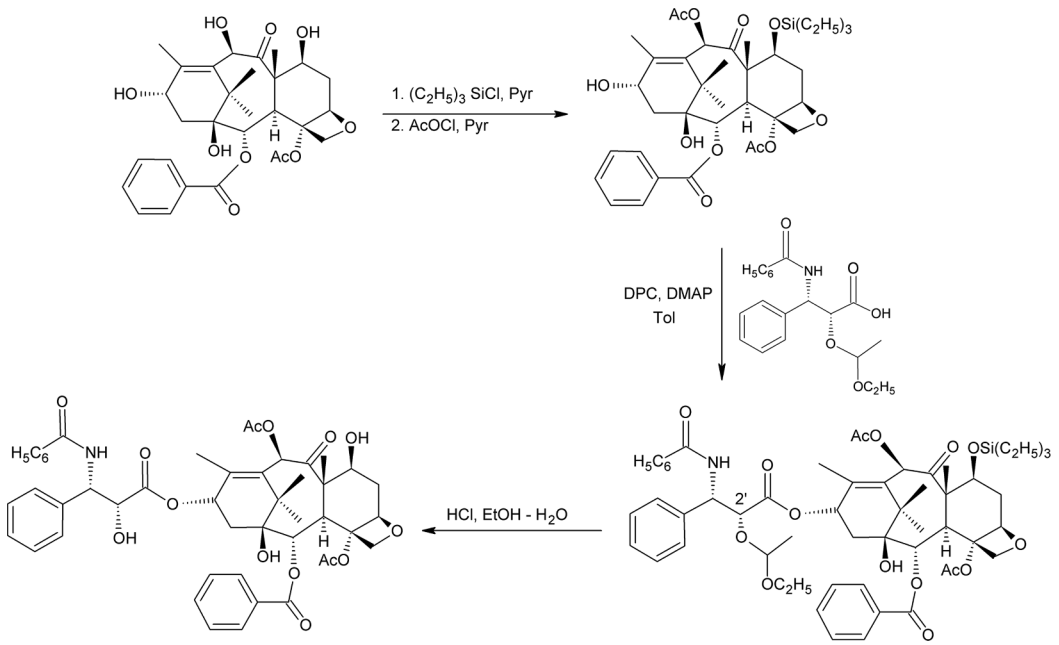


FIGURE 1.2 Scheme of paclitaxel semi-synthesis.

Copalic acid (*ent*-8-(17)-13*E*-labdadien-15-oic) is a biomarker from copaiba oils (*Copaifera* sp.), a diterpene observed in all species but mainly in *Copaifera multijuga* Hayne (da Veiga Jr. et al., 1997; Cascon and Gilbert, 2000). It was first isolated from another Brazilian oil resin, named Brazilian Copal (*Hymenaea courbail* L.), in 1961, by Carl Djerassi (Nakano and Djerassi, 1961).

Cativic acid (7-labden-15-oic) is another commonly observed diterpene in copaíba oils (da Veiga Jr. and Pinto, 2002). It was discovered in 1938, when Kalman began to study a Central America resin, *Priora copaifera*, Griseb, known by local indigenous as captive tree (Kalman, 1938).

Labdanes can be converted into clerodanes and many other skeletons. The term clerodane has its origin in a substance named clerodin, the first diterpene identified with this skeleton, isolated from *Clerodendron infortunatum* (Maciel et al., 2006).

An example of clerodane diterpene resinoic acid present in copaiba oils is clorechinic acid (*ent*-15,16-epoxi-13(16),14-clerodadiene-18-oic), a minoritary constituent in *C. cearensis* and *C. langsdorffi* copaiba oil resins (da Veiga Jr. and Pinto, 2002). It was first isolated by J. D. Phillipson, in 1993, in Equator, from the sap of *Croton lechleri* (Euphorbiceae), popularly named 'Sangue del Drago' (Chen et al., 1993). Medicinal use of this sap was related to European explorers by Mexican, Peruvian and Equadorian indigenous people since 1600 (Gupta et al., 2016).

1.2.1.3 Triterpenes

The triterpenes make up another class of terpenes with several descriptions of bioactivity, from digitalic cardiotonic glycosides and saponins to the recently observed action of betulinic acid derivatives in HIV. They are very common in plant extracts from the families Celastraceae and Rubiaceae but are abundantly produced in resins from the botanical family Burseraceae. About 4,000 triterpenes have been described, isolated from natural sources, mainly from plants. The biological activities are wide, from antimicrobial and anti-tumour, to analgesic and anti-inflammatory (Santos et al., 2016). Some pentacyclic alcohols, such as lupeol and the amyrins, have a huge incidence in resins from the Burseraceae family, including the genera *Protium* and *Bursera*. The ancient oil resins from these genera are known in human history as incense and myrrh, with several pharmacological properties already studied, mainly the anti-inflammatory and anticancer properties (Maia et al., 2000; Santos et al., 2016).

Betulinic acid is a derivative from betulin, initially observed in *Betula pendula* and related species. Together with ursolic and oleanolic acids, these acids have increased economic importance in chemotherapy as chemopreventives and antimicrobials, with several structural derivatives showing activity in cancer and HIV (Yogeeswari and Sriram, 2005; Silva et al., 2014; Santos et al., 2016).

1.2.2 Synthetic Sources

Natural products have been an important platform for producing new bioactive molecules through structural modifications. Synthetic derivatives can be produced in several steps from very simple molecules, achieving complex molecules or making only some changes in a similar molecule (sometimes very complex changes) to modify its solubility, or the kinetics of absorption of a drug, or to increase its potency. The production of synthetic derivatives aims (i) to address the demand for natural molecules with relevant therapeutical applications, such as Taxol® (paclitaxel); (ii) to substitute for some raw materials (mainly marine) of natural origin that are produced in very low yield; or (iii) to reduce production costs and time while keeping the same quality as the molecule of natural origin (Correia et al., 2002). The comprehension of the mechanisms of the chemical reactions and conformational analysis has contributed to a better understanding of molecule reactivity. In addition, the development and expansion of non-destructive analytical methods with improved sensibility, have contributed in unequivocal ways to the advance of organic synthesis (Correia et al., 2002). One of the most important events in synthetic chemistry related to natural compounds, which created biochemistry, was the urea synthesis by Frederich Wohler in 1828, the very first organic substance produced synthetically (Meessen, 2014).

Paclitaxel, a diterpene with a taxane skeleton, is nowadays the most widespread and well-known terpenoid, with therapeutical importance to thousands of people with cancer. Originally discovered in a rare species of yew, paclitaxel was extracted from the trunk bark of the *Taxus brevifolia* Nutt tree, but the very low yield, the need for the tree to be mature to produce higher amounts of the target molecule and the molecule's very complex structure made the natural extraction as difficult as the total synthesis to address the amounts needed to treat thousands of people with cancer. The endeavour was huge for natural products and synthetic chemists, but a middle-way solution appeared with the semi-synthesis of the molecule (Corrêa, 1995).

The complex approach to the synthesis of this molecule relies mainly on the B ring, but producing the taxane skeleton and introducing the lateral chain were also challenges that were faced by synthetic chemists. The construction of A and C rings was not obtained without a great number of difficult steps, resulting in a very low global yield (Elmore and Paquette, 1993; Jackson and Shea, 1994; Swindell et al., 1994). In 1981, the Denis research group achieved the semi-synthesis of paclitaxel. It was developed using as raw material a molecule that is similar to paclitaxel that was recently isolated from the leaves of another *Taxus* species, *T. baccata*. The molecule, de-acetyl-10-baccatin III, made it feasible to synthetically produce huge amounts of paclitaxel with only a few steps. The main process, with a more than 50% yield, constituted only a simple modification of the de-acetyl-10-baccatin III structure: the coupling of the lateral chain to carbon 13 and the acetylation of carbon 10 (Denis et al., 1988).

Linalool synthesis was another interesting achievement in natural products. The first studies were performed in the 1960s; however, without selectivity, the isolation procedures were very expensive. The main methodologies used prenilation catalysed by organometalic reagents (Nair and Pandit, 1966; Takabe et al., 1975; Nederlof et al., 1977; Semikoleno et al., 2001). The pinene use was very successful, with hydrogenation under Pd/C, yielding a pinane that was subsequently oxidized, resulting in the hydroperoxide which then was further hydrogenated to pinanol and isomerized to linalool (Semikolenov et al., 2001).

Another synthetic route to produce linalool was performed using citral as the raw material, a monoterpene aldehyde. The essential oil rich in citral (mainly from lemongrass) was treated with hydrogen peroxide to result in the citral-α,β-epoxide. When this product was treated with hydrated hydrazine, it resulted in the hydrazone that rearranged in acetic acid to yield linalool (Nair and Pandit, 1966).

In monoterpene chemistry, pinenes are the terpenoids most often used to synthesise other industrially important substances such as camphor, carvone, verbenol, terpinolene and *p*-cimene (Sell, 2003; Mercier et al., 2009).

1.3 Milestone in Terpenoids Discovery

1.3.1 Gibberellins

Gibberellins are terpenes that work as vegetal hormones. They were discovered by the Kurosawa research group in Japan around 1926, who were studying rice and fungi such as *Giberella fujikuroi*. The fungi made the plants very weak, yet some plant parts were able to grow very rapidly. In 1938, the active substances from this fungus were isolated by Yabuta and Sumiki and named gibberellins A and B. In the United States and the United Kingdom, the studies performed during the 1950s resulted in the isolation of gibberellic acids (GA3). In plants, the first gibberellin was isolated only in 1958, from *Phaseolus coccineus*.

This vegetal growth hormone can be found in angiosperms, gymnosperms, fungi, algae and even in some bacteria. More than 130 different gibberellins are already described in the literature, but only a few are biologically active (Zeny and Trojan, 2016). They are related to diterpenes, with 20 or 19 carbons, with the last being the more active.

Gibberellins are observed mature plants in very low concentrations relative to immature seeds. The synthetic process takes place in seeds as well as in developing fruits and young leaves. It takes place

in three cellular compartments: the cytoplasm, plasmids and endoplasmic reticulum. When the synthesis takes place in leaves, the transport is via the phloem. The gibberellins function in controlling some aspects of the development and growth of plants and their response to environmental aspects. GA3 is a very common bioactive gibberellin. The fungi *G. fujikuroi* is nowadays the used as the main producer of this hormone in industry. Alternative sources have been from sugarcane to fruits and lettuce production (Epifânio and Pinto, 1990).

1.3.2 Sesquiterpene Lactones

Sesquiterpene lactones are a group of terpenes with a wide spectrum of biological activities. They are described mainly in the Asteraceae, Acanthaceae, Anacardiaceae, Apiaceae, Euphorbiaceae, Lauraceae, Magnoliaceae botanical families and present insecticide, fungicide and bactericide activities.

Artemisinin, a sesquiterpene lactone from the Chinese plant *Artemisia anua*, is bioactive to malaria and also cytotoxic to several *Plasmodium* species (De Carvalho and da Fonseca, 2006). Another 12 sesquiterpene lactones have been isolated from this species, but none of those show the same bioactivity; however, anti-tumour compounds from this class have been described in the literature (De Carvalho and da Fonseca, 2006). In several models of cytotoxicity in tumour cells, sesquiterpene lactones have inhibited tumour growth. Kupchan and co-workers found the effect of the exocyclic double bond conjugated with the γ-lactone to be responsible for this cytotoxic effect (Rodriguez et al., 1976).

1.3.3 Forskolin

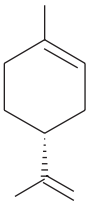
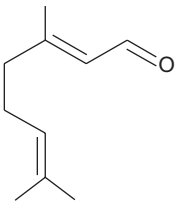
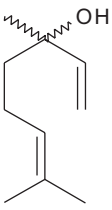
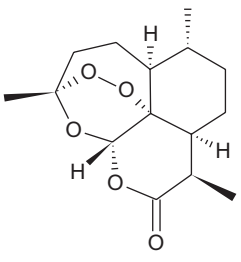
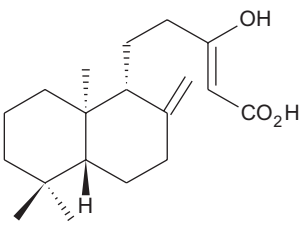
The genus *Coleus* is an important source of bioactive plants in Hindu traditional medicine. Extracts from this species have applications in convulsive to cardiac problems, from abdominal pain to insomnia. Several research studies that were performed by the Central Drug Research Institute (CDRI) in Lucknow and by Hoechst Pharmaceuticals—with the species *Coleus forskohlii*, after some misunderstanding about the correct chemical structure, initially called coleonol—have led to the identification of the diterpene forskolin as the main compound responsible for the biological activities (Ammon and Muller, 1985). The species *Coleus forskohlii* has its origin in Africa, is being cultivated in India and in Brazil, where its importance as a medicinal plant can be evaluated by the number of different cultivars of this plant found in popular medicine: *boldo*, *malva santa*, *sete-dores* and *tapete-de-Oxalá* (which is one of the most cited medicinal plants in ethnobotanical studies in Brazil) (Costa, 2006). Indeed, chromatographic analysis performed in Africa, India and Brazil has shown a varied chemical profile that differs in each region, sometimes with no forskolin being detected, and sometimes only in young plants at less than 1 year of age (Costa, 2006). The biological properties of forskolin were described by Dubey et al. (1981), who highlighted the cardiovascular effects of lower blood pressure and improved cardiac rhythm (Ammon and Muller, 1985). Anti-inflammatory effects are also described in the literature (Costa, 2006).

1.3.4 Ginkgolides

Ginkgo biloba (*Ginkgoaceae*) is an Asian species, with old, disease-resistant trees. Since 1965, extracts from Gingko have been commercialised in the Western world under the name EGb 761 and indicated for central nervous system and cardiovascular diseases (Leandro et al., 2012). The interests in Gingko rapidly spread and several biological and chemical studies were performed. Interestingly, two main groups, the flavonoids (24%) and the terpenes (6%), were observed; they are sesquiterpene lactones (known as bilobalides) and diterpene lactones (ginkgolides, named A, B, C, M and J) (Forlenza, 2003; Carla et al., 2007). Ginkgolides are now used in acute inflammation and asthma as well as in antirejection transplant factors for their action on plaquetary aggregation (Carla et al., 2007; Passos et al., 2009) (Table 1.1).

TABLE 1.1

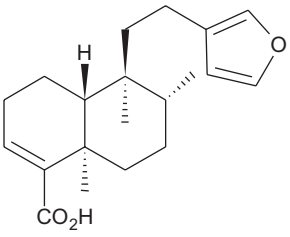
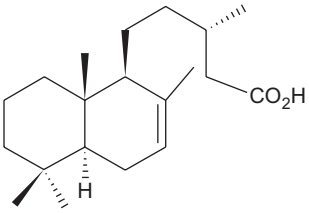
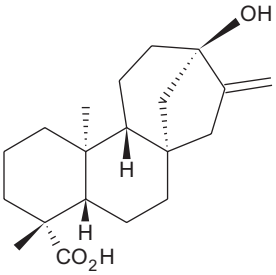
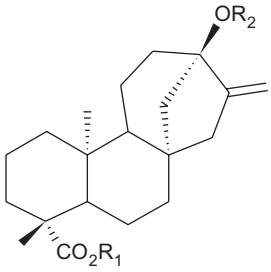
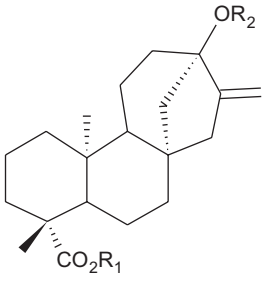
Terpenoids of Commercial Relevance and Their Main Chemical Properties

Name	Chemical Structure	Properties
α-Pinene		Monoterpene ($C_{10}H_{16}$) M.W.: 136.238 g/mol Nonpolar liquid Boiling point: 156.0°C
β-Pinene		Monoterpene ($C_{10}H_{16}$) M.W.: 136.238 g/mol Nonpolar liquid Boiling point: 166.0°C
D-Limonene		Monoterpene ($C_{10}H_{16}$) M.W.: 136.238 g/mol Nonpolar liquid Boiling point: 175.4°C
Citral		Oxygenated monoterpene ($C_{10}H_{16}O$) M.W.: 152.237 g/mol Nonpolar liquid Boiling point: 229.0°C
Linalool		Oxygenated monoterpene ($C_{10}H_{18}O$) M.W.: 154.253 g/mol Nonpolar liquid Boiling point: 198.5°C
Artemisinin		Sesquiterpene lactone ($C_{15}H_{22}O_5$) M.W.: 282.336 g/mol Polar liquid Boiling point: 389.9°C
Copalic acid		Diterpenic acid ($C_{20}H_{32}O_2$) M.W.: 304.474 g/mol Polar solid Boiling point: 416.6°C

(*Continued*)

TABLE 1.1 (*Continued*)

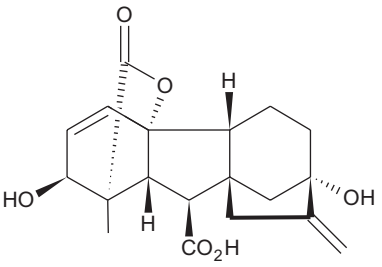
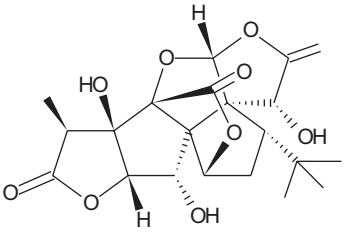
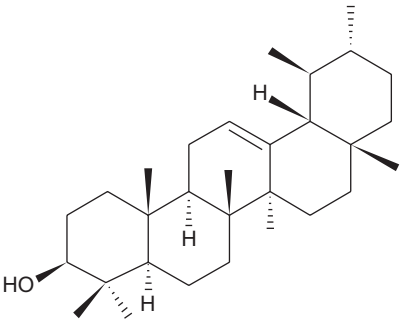
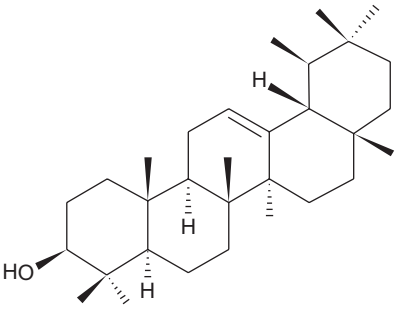
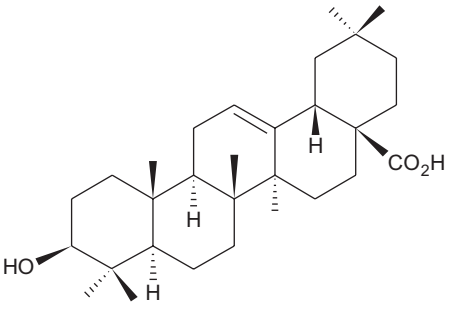
Terpenoids of Commercial Relevance and Their Main Chemical Properties

Name	Chemical Structure	Properties
Hardwickiic acid		Diterpenic acid ($C_{20}H_{28}O_3$) M.W.: 316.441 g/mol Polar solid Boiling point: 427.2°C
Cativic acid		Diterpenic acid ($C_{20}H_{34}O_2$) M.W.: 306.483 g/mol Polar solid Boiling point: 408.5°C
Steviol		Diterpene ($C_{20}H_{30}O_3$) M.W.: 318.450 g/mol Boiling point: 464.5°C
Stevioside	 R_1 = β-Glu R_2 = β-Glu-β-Glu (2→1)	Glycosylated diterpene ($C_{38}H_{60}O_{18}$) M.W.: 804.872 g/mol Boiling point: 963.3°C
Rebaudioside A	 R_1 = β-Glu R_2 = β-Glu-β-Glu-β-Glu (3→1)	Glycosylated diterpene ($C_{44}H_{70}O_{23}$) M.W.: 967.013 g/mol Boiling point: 1102.8°C

(*Continued*)

TABLE 1.1 (*Continued*)

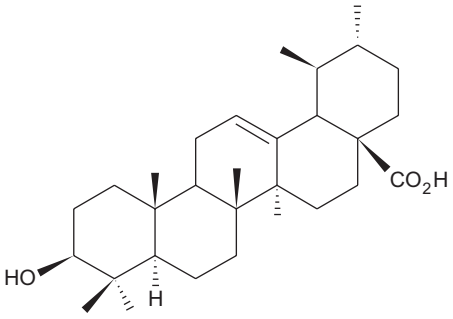
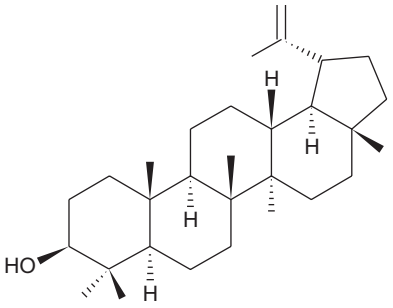
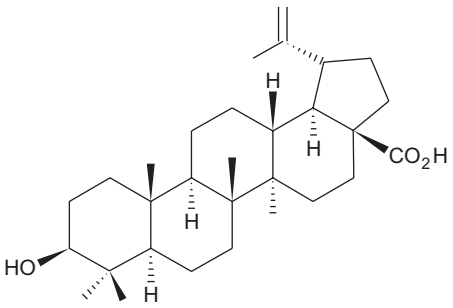
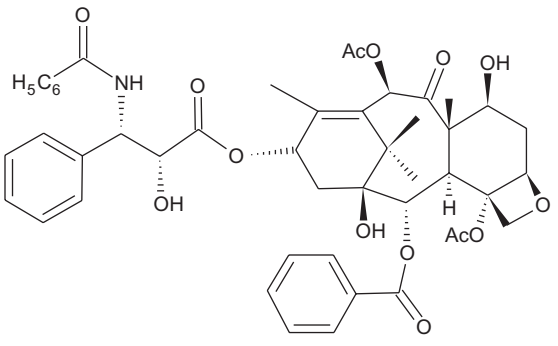
Terpenoids of Commercial Relevance and Their Main Chemical Properties

Name	Chemical Structure	Properties
Gibberellic acid (GA3)		Pentacyclic diterpene ($C_{19}H_{22}O_6$) M.W.: 346.374 g/mol White solid Boiling point: 628.6°C
Ginkgolide B		Diterpenic lactone ($C_{20}H_{24}O_{10}$) M.W.: 424.402 g/mol Polar Boiling point: 762.4°C
α-Amyrin		Pentacyclic triterpene ($C_{30}H_{50}O$) M.W.: 426.717 g/mol Polar solid Boiling point: 493.8°C
β-Amyrin		Pentacyclic triterpene ($C_{30}H_{50}O$) M.W.: 426.717 g/mol Polar solid Boiling point: 490.7°C
Oleanolic acid		Pentacyclic triterpene ($C_{30}H_{48}O_3$) M.W.: 456.711 g/mol Polar solid Boiling point: 553.5°C

(*Continued*)

TABLE 1.1 (*Continued*)

Terpenoids of Commercial Relevance and Their Main Chemical Properties

Name	Chemical Structure	Properties
Ursolic acid		Pentacyclic triterpene ($C_{30}H_{48}O_3$) M.W.: 456.711 g/mol Polar solid Boiling point: 556.9°C
Lupeol		Pentacyclic triterpene ($C_{30}H_{50}O$) M.W.: 426.729 g/mol Polar solid Boiling point: 488.1°C
Betulinic acid		Pentacyclic triterpene ($C_{30}H_{48}O_3$) M.W.: 456.711 g/mol Polar solid Boiling point: 550.0°C
Paclitaxel		Diterpene ($C_{47}H_{51}NO_{14}$) M.W.: 853.918 g/mol Polar solid Boiling point: 957.1°C

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