

## TERPENES : structural classification and biological activities

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### Abstract

Terpenes is a large group of compounds found in flowers, stems, leaves, roots and other parts of numerous plant species. They are built up from isoprene units with the general formula  $(C_5H_8)_n$ . They can be grouped into classes according to the number of isoprene units ( $n$ ) in the molecule: hemiterpenes ( $C_5H_8$ ), monoterpenes ( $C_{10}H_{16}$ ), sesquiterpenes ( $C_{15}H_{24}$ ), diterpenes ( $C_{20}H_{32}$ ), triterpenes ( $C_{30}H_{48}$ ), tetraterpenes ( $C_{40}H_{64}$ ), and polyterpenes  $(C_5H_8)_n$ . Most of the terpenoids with the variation in their structures are biologically active and are used worldwide for the treatment of many diseases. Many terpenoids inhibited different human cancer cells and are used as anticancer drugs such as Taxol and its derivatives. Many flavorings and nice fragrances are consisting on terpenes because of its nice aroma. Terpenes and its derivatives are used as antimalarial drugs such as artemisinin and related compounds. Meanwhile, terpenoids play a diverse role in the field of foods, drugs, cosmetics, hormones, vitamins, and so on. This chapter provides classification, biological activities and distribution of terpenes isolated currently from different natural sources.

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### I. Introduction

There are many different classes of naturally occurring compounds. Terpenes also form a group of naturally occurring compounds majority of which occur in plants, a few of them have also been obtained from other sources [1]. They are a large class of natural hydrocarbon secondary metabolites built up from five-carbon isoprene units linked together most commonly in a head-to-tail arrangement, but can be constructed in other configurations with varying degrees of unsaturation, oxidation, functional groups and ring closures, giving rise to a rich diversity of structural classes, with novel skeletons being continuously discovered [1,2]. These modified hydrocarbons are referred to as terpenoids, which are primarily found to occur in a wide variety of higher plants. They can also be found in some insects and marine organisms. They are volatile substances which give plants and flowers their fragrance [1]. The name, terpene, is derived from the word turpentine, a product of coniferous oleoresins. The terpenes and terpenoids (terpene like compounds) are classified or grouped according to the number of isoprene units found in the parent nucleus, ranging from one to many.

The biological activity profiles of the terpenoids are diverse and defy simple categorization, with the possible exception of the sesquiterpene lactones, which are well known for being cytotoxic natural products. However, artemisinin, a sesquiterpene lactone endoperoxide, is an important antimalarial drug with high activity against the multidrug-resistant form of *Plasmodium falciparum*. A number of diterpenoids are well known for their biological/pharmacological/therapeutic effects. Among the bioactive diterpenes are ginkgolides (PAF inhibitors), gibberellins (plant growth hormones), phorbol esters (tumor promoters), and the anti-cancer agent, paclitaxel [3]. Members of the triterpenoids are biologically active, among which are the ginsenosides (adaptogens), betulinic acid (anti-melanoma), brusatol (chemopreventive), and boswellic acids (anti-inflammatory and anti-arthritis) [4]. As cited in the sections to follow, many other terpenoids possess interesting and diverse biological activities and therapeutic potentials, biological tools or lead compounds for drug discovery research. Chemical and biological studies have shown that the terpenoids possess a variety of chemical, physical and biological activities [5]. Because of their vast numbers (more than 30,000) and their different physical, chemical and biological properties, it is not possible to provide a comprehensive treatise on all of the different groups of terpenoids in this chapter. Rather, a select number of the largest and most commonly encountered groups of terpenoids, will be discussed from the chemical and biological perspective in the following sections.

## II. Classification

### II.1. Isoprene Rule

About 30 000 terpenes are known at present in the literature. Thermal decomposition of terpene give isoprene as one of the product. Otto Wallach pointed out thatterpenoids can be built up of isoprene unit. Their basic structure follows a general principle: 2-Methylbutane residues, less precisely but usually also referred to as isoprene units,  $(C_5)_n$ , build up the carbon skeleton of terpenes; this is the isoprene rule found by Ruzicka. Special isoprene rule states that the terpenoid molecule is constructed of two or more isoprene units joined in a « *head to tail* » fashion[6-9]. But this rule can only be used as guiding principle and not as a fixed rule. For example carotenoids are joined « *tail to tail* » at their central and there are also some terpenoids whose carbon content is not a multiple of five [10]. In applying isoprene rule we look only for the skeletal unit of carbon. The carbon skeletons of open chain monoterpenoids and sesquiterpenoids are, Ingold (1921) pointed that a gem alkyl group affects the stability of terpenoids. He summarized these results in the form of a rule called « gem dialkyl rule » which may be stated as Gem dialkyl group tends to render the cyclohexane ring unstable where as it stabilizes the three, four and five member rings.” This rule limits the number of possible structure in closing the open chain to ring structure. Thus the monoterpenoid open chain give rise to only one possibility for a monocyclic monoterpenoid i.e the *p*-cymene structure [10]. Therefore, terpenes are also denoted as isoprenoids. In nature, terpenes occur predominantly as hydrocarbons, alcohols and their glycosides, ethers, aldehydes, ketones, carboxylic acids and esters [10].

### II.2. Classification

Terpenes can be grouped into classes according to the number of isoprene units (n) in the molecule : hemiterpenes ( $C_5H_8$ ), monoterpenes ( $C_{10}H_{16}$ ), sesquiterpenes ( $C_{15}H_{24}$ ), diterpenes ( $C_{20}H_{32}$ ), triterpenes ( $C_{30}H_{48}$ ), tetraterpenes ( $C_{40}H_{64}$ ), and polyterpenes ( $(C_5H_8)_n$ ) (Table 1)[11]. Most of the terpenoids with the variation in their structures are biologically active and are used worldwide for the treatment of many diseases. Many terpenoids inhibited different human cancer cells and are used as anticancer drugs such as Taxol and its derivatives. Many flavorings and nice fragrances are consisting on terpenes because of its nice aroma. Terpenes and its derivatives are used as antimalarial drugs such as artemisinin and related compounds. Meanwhile, terpenoids play a diverse role in the field of foods, drugs, cosmetics, hormones, vitamins, and so on[11].

**Table 1** : Classification of terpenes

Number of carbon atoms	Value of n	Class
5	1	Hemiterpenes ( $C_5H_8$ )
10	2	Monoterpenes ( $C_{10}H_{16}$ )
15	3	Sesquiterpenes ( $C_{15}H_{24}$ )
20	4	Diterpenes ( $C_{20}H_{32}$ )
25	5	Sesterpenes ( $C_{30}H_{48}$ )
30	6	Triterpenes ( $C_{30}H_{48}$ ),
40	8	Tetraterpenes ( $C_{40}H_{64}$ )
>40	>8	Polyterpenes ( $(C_{40}H_{64})_n$ )

#### II.2.1. Hemiterpenes

Hemiterpenes are the simplest terpenes. The number of known hemiterpene aglycones is less than 100. Most of them occur as oils, and mostly water insoluble, but some sugar containing molecules are water soluble [12]. These compounds can be found in different plant parts. The best known hemiterpene is isoprene (**1**), which is the basic unit of all terpenes. Tiglic (**3**), caffeic (**4**) and isovaleric (**5**) acids are examples of well known naturally occurred hemiterpenes found in plants (Figure 1) [12,13].

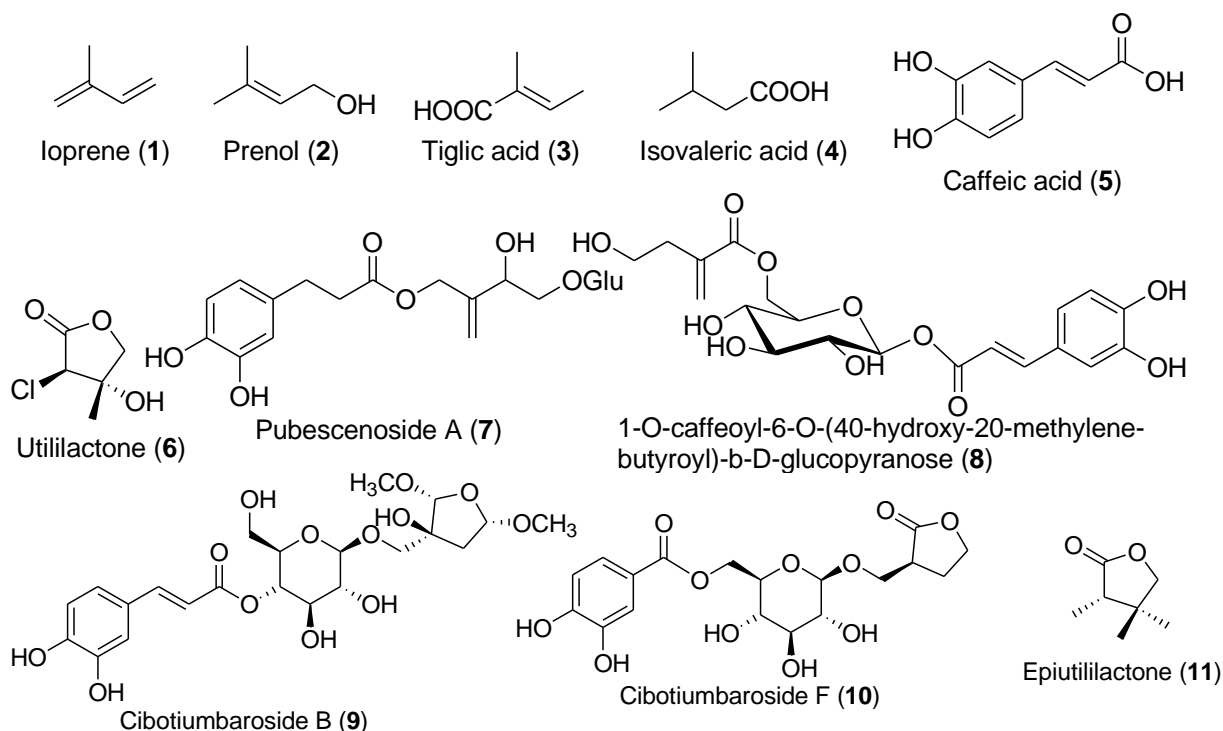


Figure 1 : Structure of some hemiterpenoids

### II.2.2. Monoterpenes

Monoterpenes consist of 10 carbon atoms with two isoprene units and molecular formula  $C_{10}H_{16}$ . They are extensively distributed in secretory tissues such as oil glands or chambers and resin canals of higher plants, insects, fungi and marine organisms. Monoterpenoids occur in more than 30 different known carbon skeletons [14]. Among them, approximately 20 are common and can be divided into acyclic, monocyclic and bicyclic types (Figures 2). Within each group, the monoterpenoids may be simple unsaturated hydrocarbons or may have functional groups and be alcohols, aldehydes, and ketones. The bicyclic monoterpenes may be divided into three classes according to the size of the second ring. The first being a six-membered ring in each class while the second can be either a three, four, or five-membered ring. Thujone and  $\Delta^3$ -carene are representatives of the group containing 6 + 3-membered rings,  $\alpha$ - and  $\beta$ -pinene represent a 6 + 4 group, while borneol and camphor, a 6 + 5 group [14]. A few typical examples are shown in Figure 2.

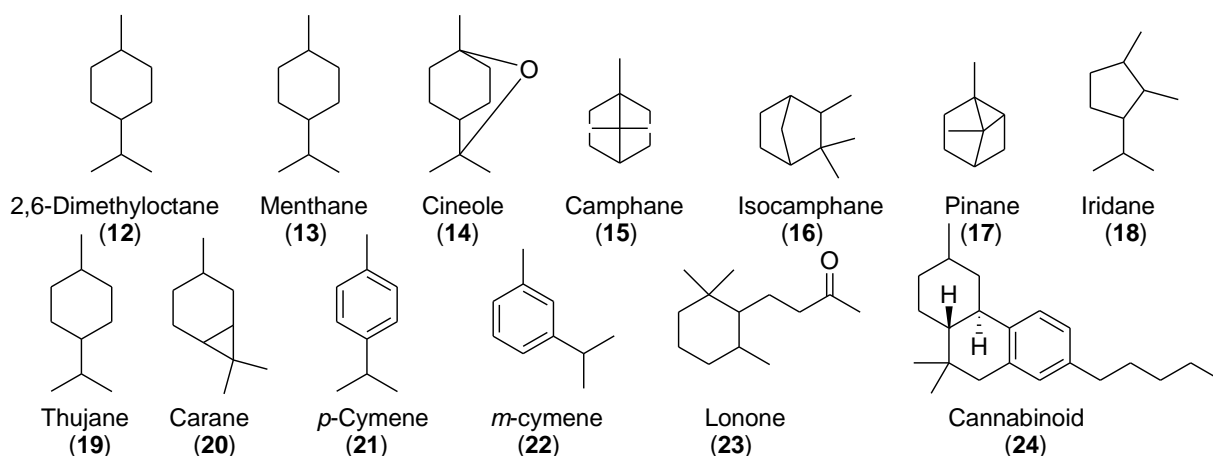


Figure 2 : Common monoterpene skeletons

Iridoids comprise a large group of monoterpenoids, characterized by skeletons in which a six-membered ring, containing an oxygen atom, is fused to a cyclopentane ring (iridane skeleton). These compounds most frequently occur in plants combined with sugar and so are classified as glycosides [15] that are further divided into four main groups. These are iridoid glycosides (aucubin, harpagoside), nonglycosylated or

simple iridoids (loganin), secoiridoids (gentiopicroside), and bisiridoids, formed by dimerization of iridoids and secoiridoids [16] (Figure 3).

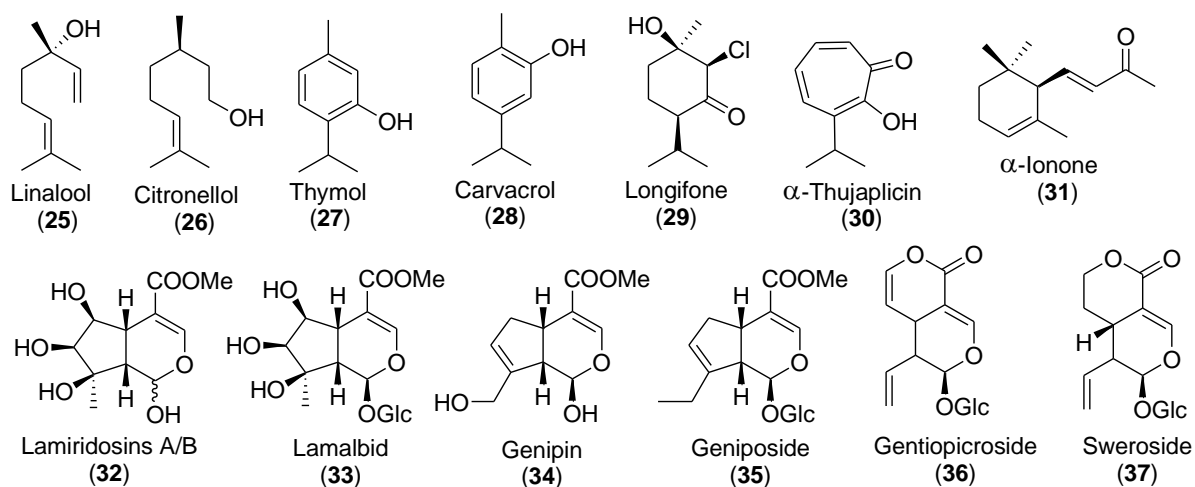
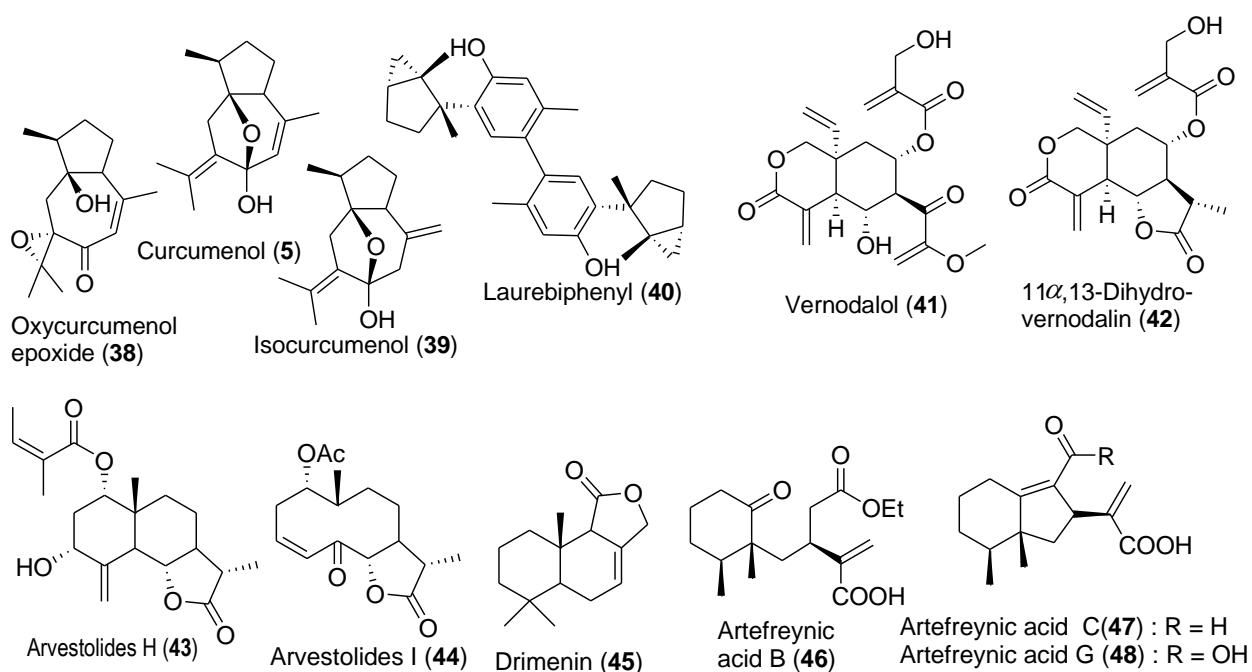


Figure 3 : Structure of some monoterpenoids

### II.2.3. Sesquiterpenes

Sesquiterpenes are the class of secondary metabolites consisting of three isoprene units ( $C_{15}H_{24}$ ) and found in linear, cyclic, bicyclic, and tricyclic forms. Sesquiterpenes are also found in the form of lactone ring. They occur in nature as hydrocarbons or in oxygenated forms including lactones, alcohols, acids, aldehydes, and ketones [17]. Sesquiterpenes also include essential oils, as well as aromatic components from plants and have numerous basic skeletons with different nomenclature. Apart from the simple farnesane and some irregular acyclic sesquiterpenoids, most sesquiterpenes have cyclic skeletons [17].



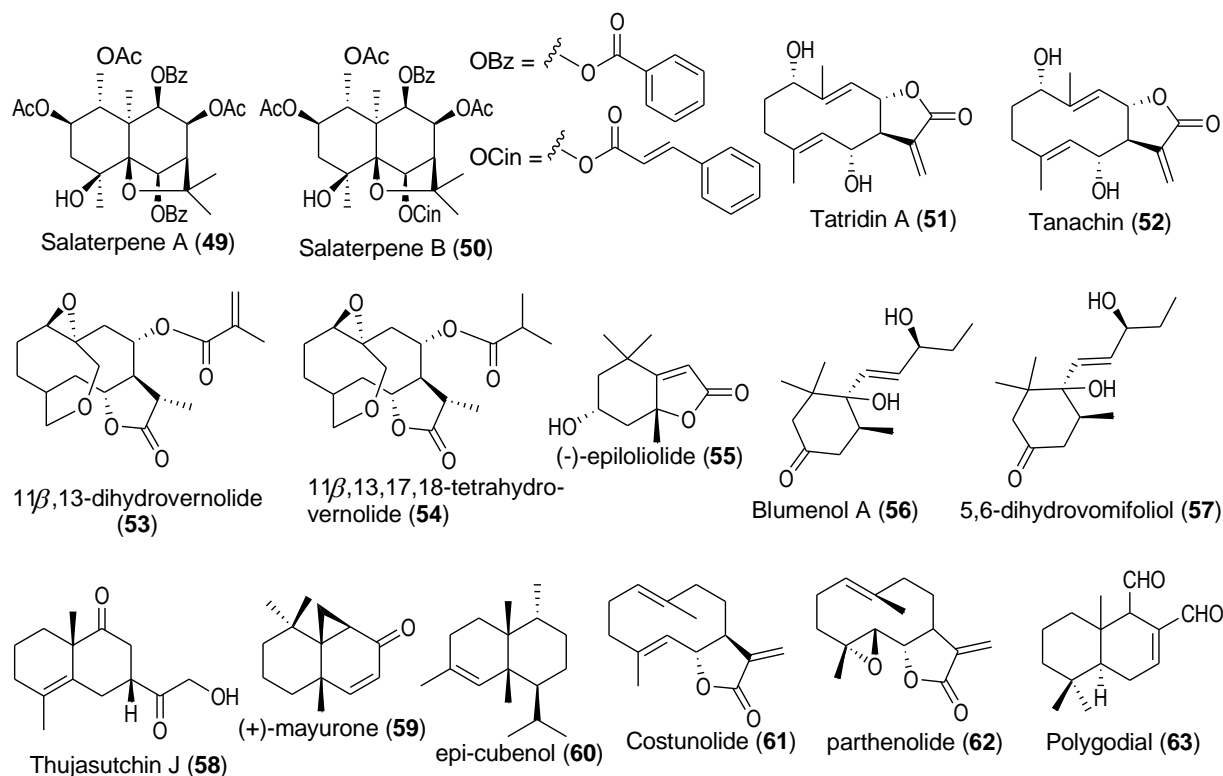
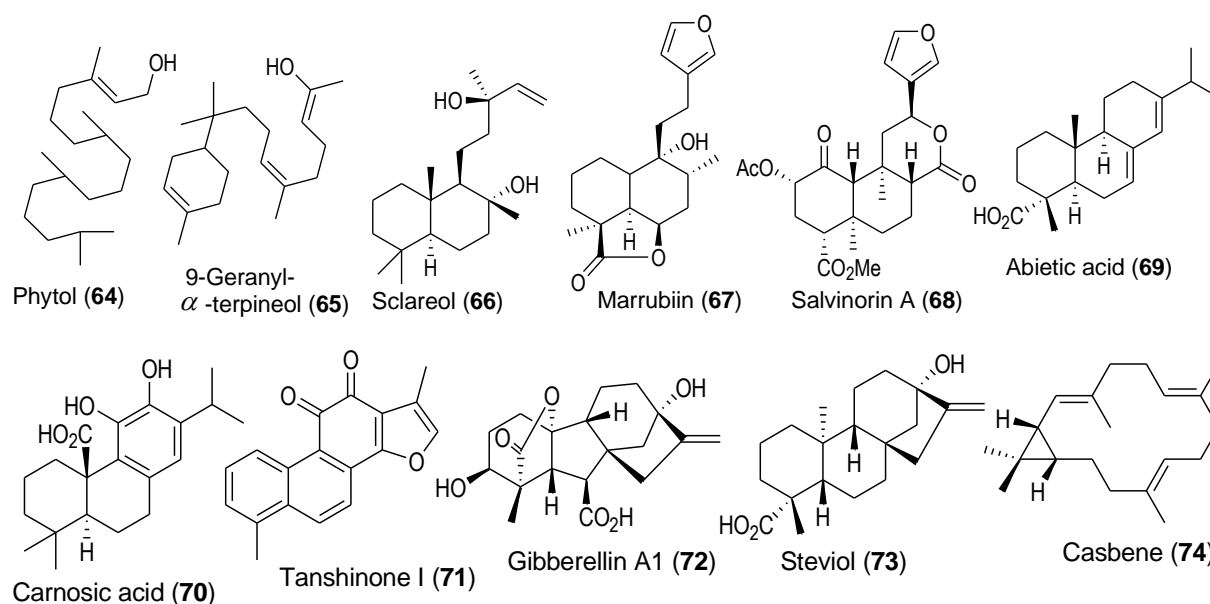


Figure 4 : Structures of some sesquiterpenoids.

#### II.2.4. Diterpenes

Diterpenoids belong to a versatile class of chemical constituents found in different natural sources having  $C_{20}H_{32}$  molecular formula and four isoprene units (Figure 4). They can be classified as linear, bicyclic, tricyclic, tetracyclic, pentacyclic, or macrocyclic diterpenes depending on their skeletal core. In nature, they are commonly found in a polyoxygenated form with keto and hydroxyl groups, these are often esterified by small-sized aliphatic or aromatic acids [18]. The representatives of each group are presented in Figure 5. Ginkgolides are unique constituents of *Ginkgo biloba* and are found exclusively in this tree. The ginkgolides are diterpenes with a cage skeleton consisting of six five-membered rings: a spiro[4.4]-nonane carbocyclic ring, three lactones, and a tetrahydrofuran ring, e.g., ginkgolide A (Figure 5) [19].



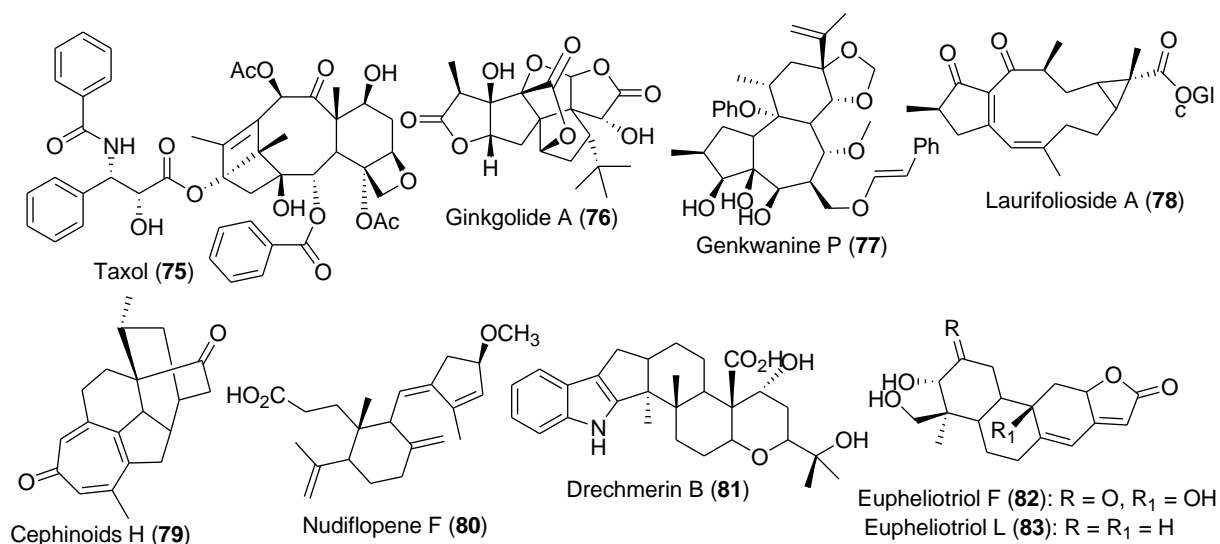
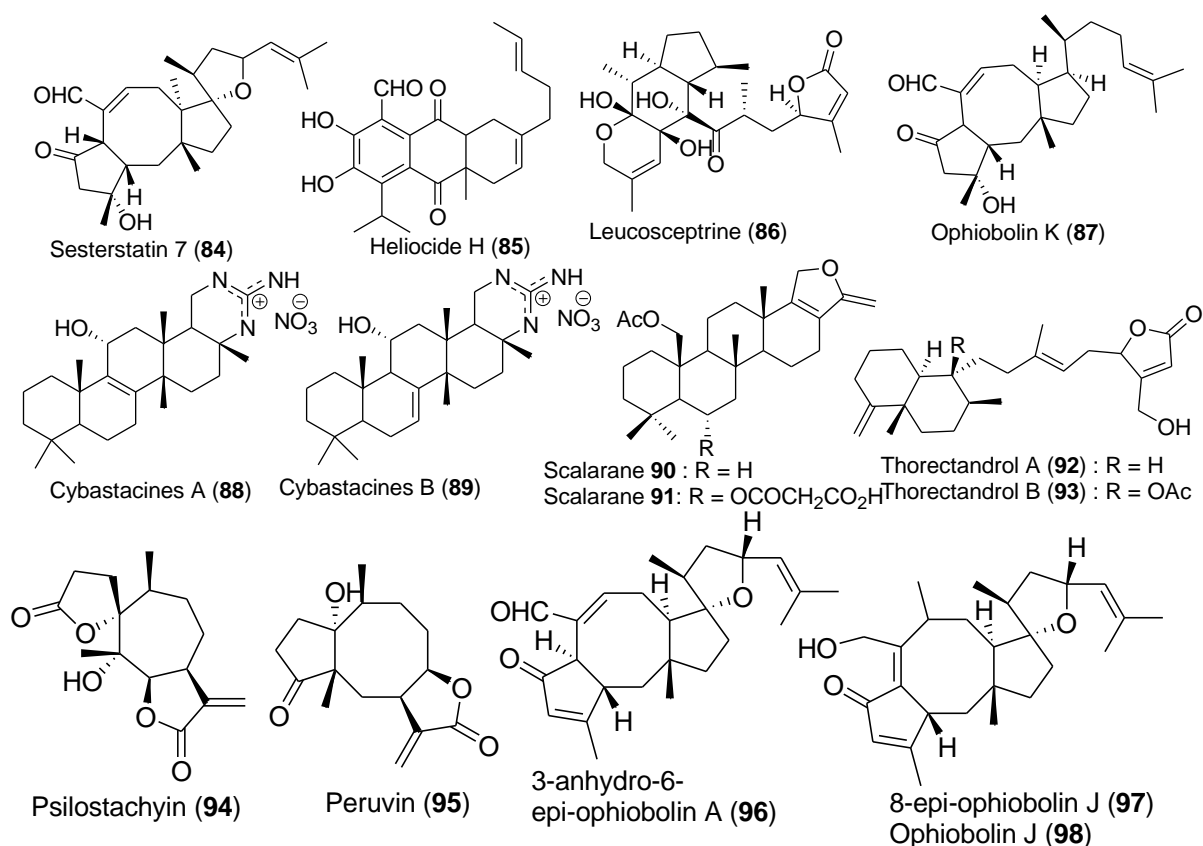


Figure 5 : Structures of some diterpenoids.

### II.2.5. Sesterterpenes

Sesterterpenes consist of 25 carbon atoms with 5 isoprene units and molecular formula  $C_{25}H_{40}$  (Figure 6). These are naturally present in the fungus, marine organism, insects, sponges, lichens, and protective waxes of insects. They exist in a wide variety of forms, including linear, monocyclic, bicyclic, tricyclic, tetracyclic, and macrocyclic frameworks [20,21]. A few typical examples are shown in Figure 6.



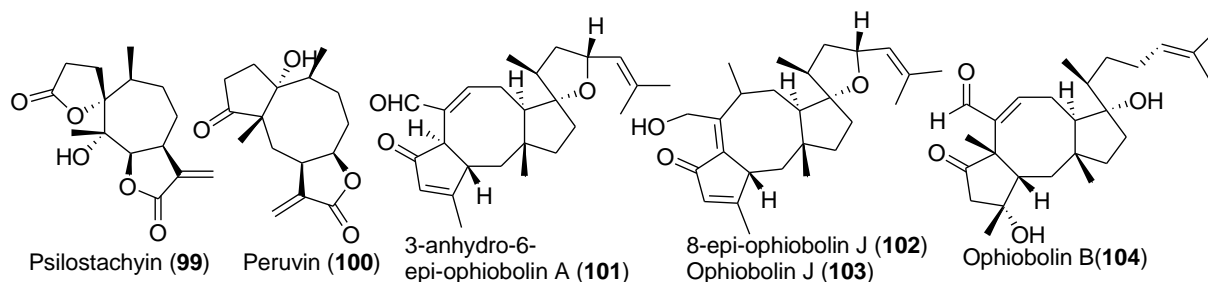
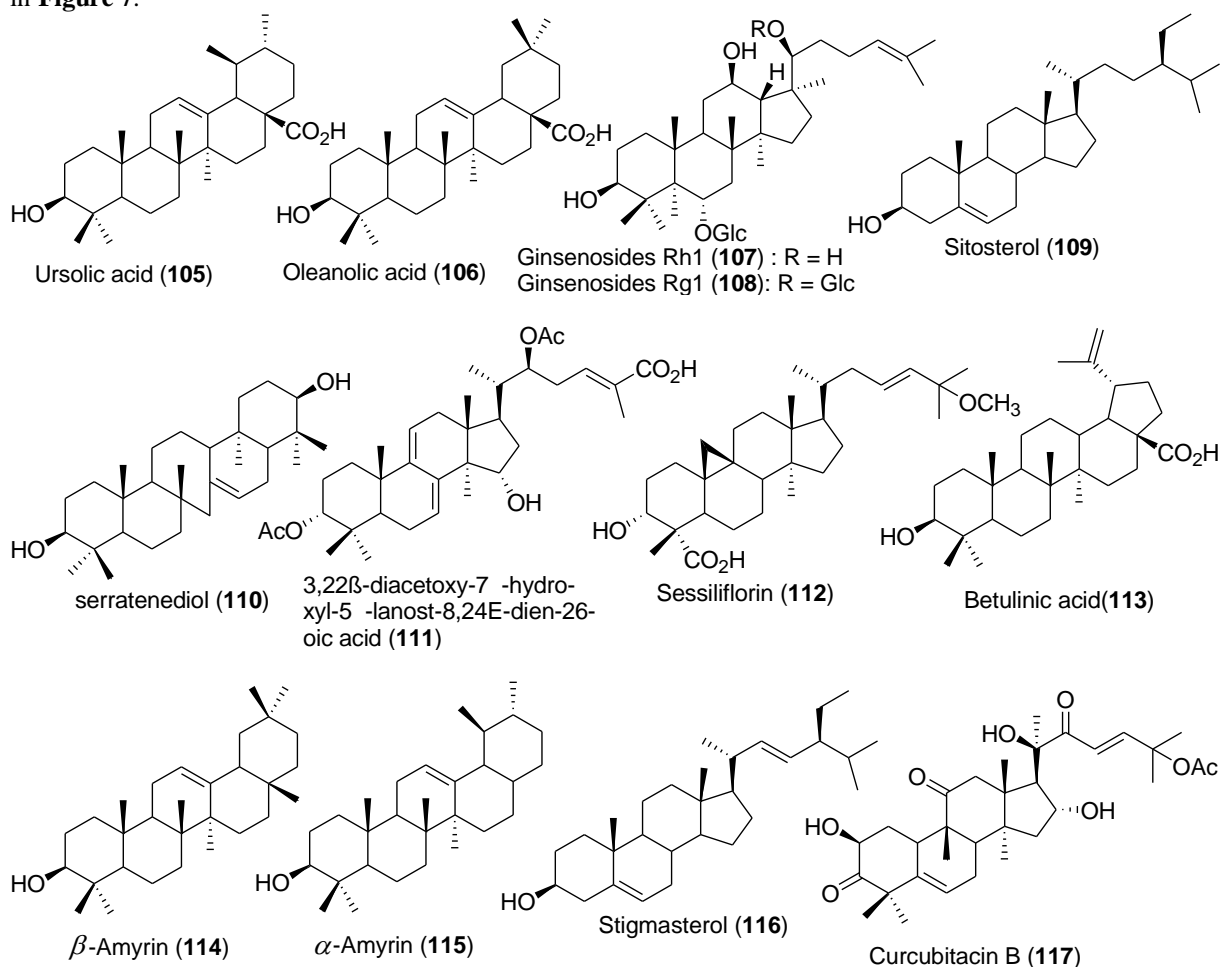


Figure 6 : Structures of some sesterterpenoids.

### II.2.6. Triterpenes

Triterpenoids are compounds with a carbon skeleton based on six isoprene units which are derived biosynthetically from the acyclic C<sub>30</sub> hydrocarbon, squalene [22]. They have relatively complex cyclic structures, most being either alcohols, aldehydes or carboxylic acids [22]. Triterpenes have many methyl groups and it can be oxidized into alcohols, aldehydes and carboxylic acids, which make it complex and differentiate it biologically. Triterpenes have many active sites for the glycosylation which converts it into another big class of compounds, namely, saponins (triterpene glycoside)[23]. The examples of most important triterpenes are shown in Figure 7.



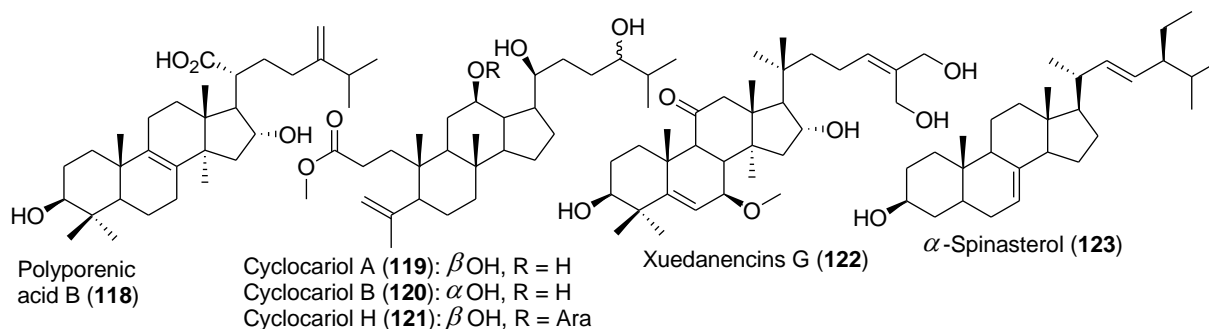


Figure 7 : Structures of some triterpenoids.

### II.2.7. Tetraterpenes

Tetraterpenoids consist of eight isoprene units and have the molecular formula  $C_{40}H_{64}$ . The most common tetraterpenoids are carotenoids, which are natural fat-soluble pigments. Structurally, carotenoids feature three aspects [24] :

- Most widely known carotenoids are either simple unsaturated hydrocarbons having the basic lycopene structure or their corresponding oxygenated analogs, known as xanthophylls (lutein, zeaxanthin) ;
- Eight isoprene units are found to be joined head to tail in lycopene (124) to give it a conjugated system that is responsible for the chromophoric characteristic of the molecule, i.e., producing color ;
- Cyclization of lycopene at both terminals of the molecule yields a bicyclic hydrocarbon commonly known as  $\beta$ -carotene (125), which occur most abundantly in higher plants. Combined forms of carotenoids occur, especially in flowers and fruits of higher plants, and they are usually xanthophylls esterified with fatty acid residues, e.g., palmitic, oleic, or linoleic acids. Glycosides are normally very rare : in higher plants, the best known in the water-soluble crocin (127), the gentiobiose derivative of an unusual C20-carotenoid, crocetin (the yellow pigment of meadow saffron, *Crocus sativus* L.) [25]. The most characteristic representatives of carotenoids are presented in Figure 8.

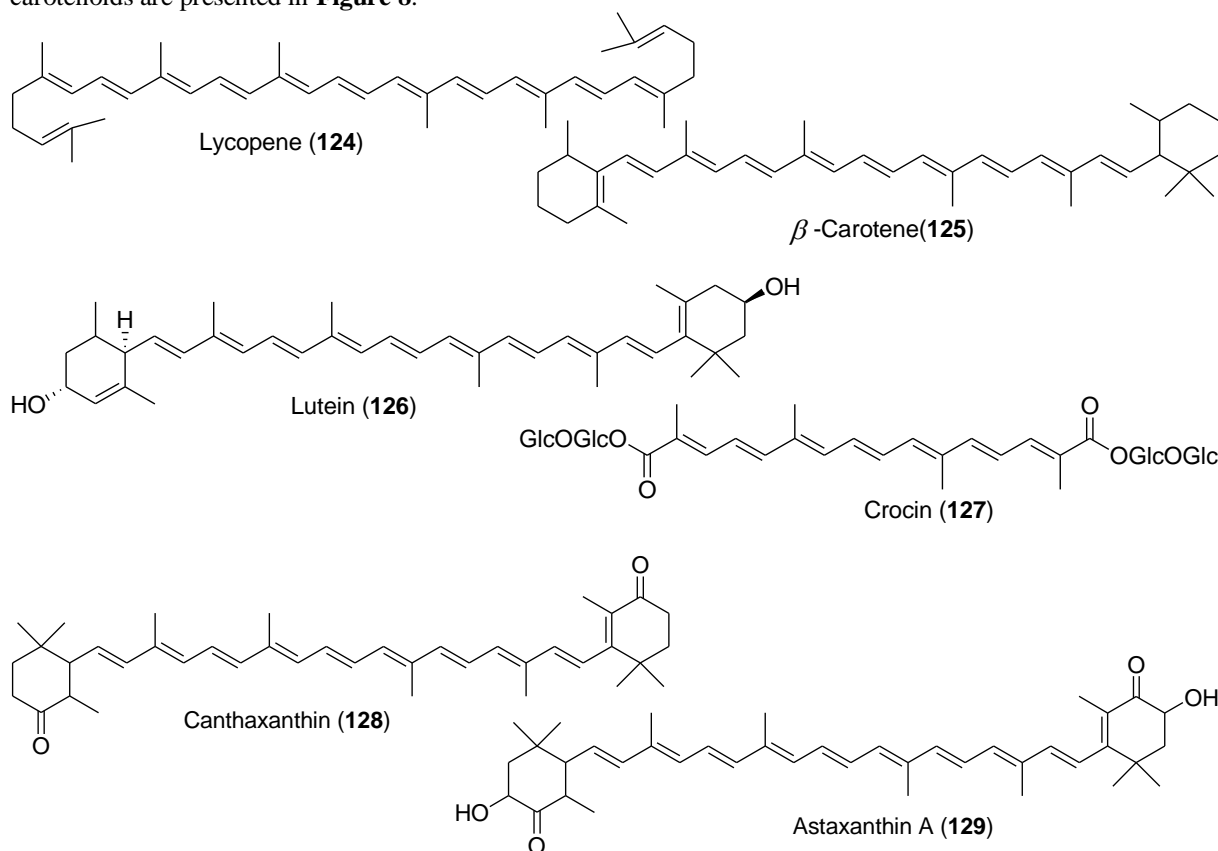


Figure 8 : Structures of some tetraterpenoids.



## II.2.8. Polyterpenes

Polyterpenoids are polymeric isoprenoid hydrocarbons, which consist of more than eight isoprene units. This class of compounds has customarily been confirmed to include the rubbers. The natural rubber molecule is a high-molecular weight polymer consisting of isoprene units in the *cis*-configuration. Some plants produce a polyisoprene with *trans* double bonds. These are gutta-percha from *Palaquium gutta* (Sapotaceae) and balata from *Mimusops balata* (Sapotaceae) (**Figure 9**) [26].



**Figure 9** : Structures of some polyterpenoids.

## II.2.9. Irregular Terpenoids

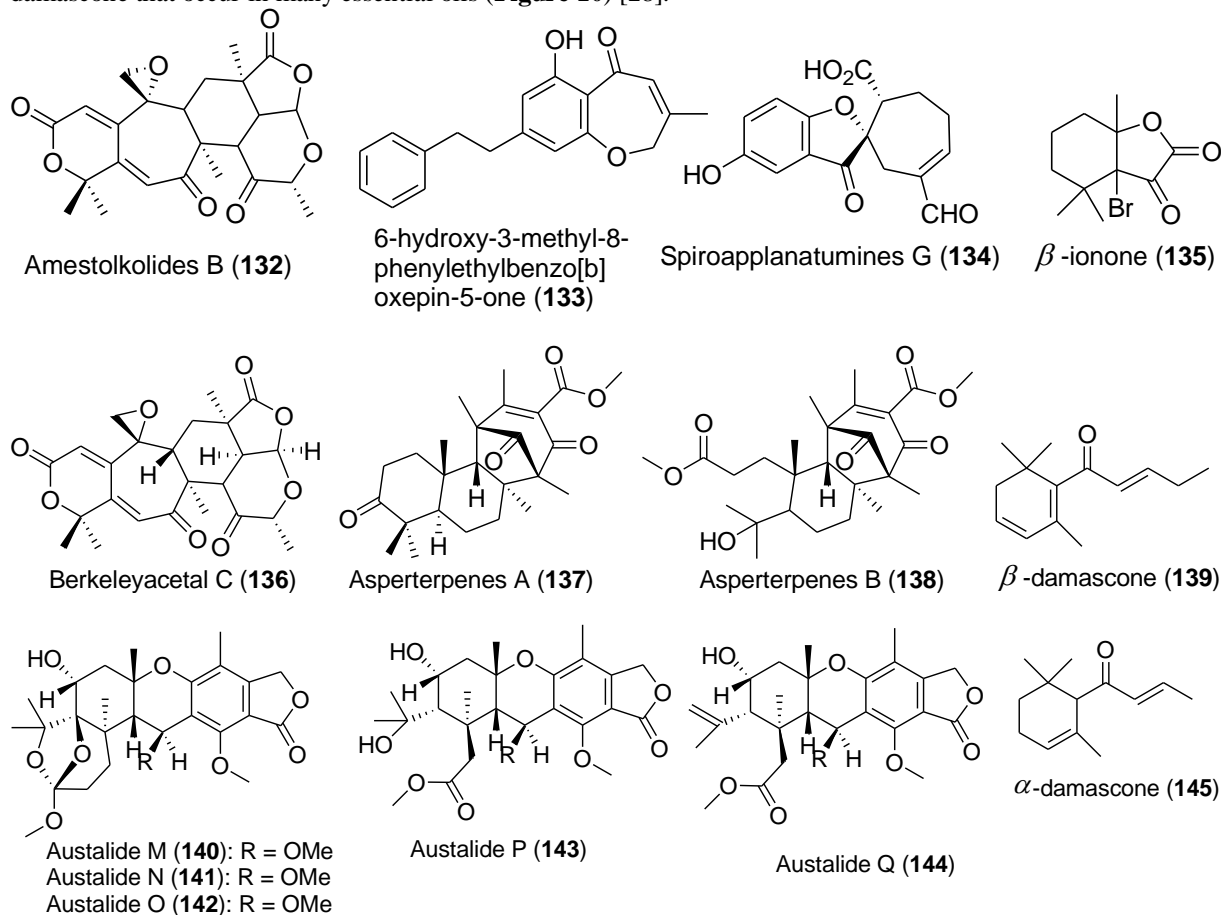
### II.2.9.1. Irregular Monoterpenoids

Two major types of irregular monoterpenoids exist :

- The substituted cycloheptane monoterpenes, called tropones. Such compounds most probably arise by an unknown ring expansion of the cyclohexane skeleton;
- Compounds formed by head-to-middle condensation of isoprene units. Important members include artemisia ketone, chrysanthemic acid, and lavandulol. These compounds are found primarily in the Asteraceae and Lamiaceae families [27] (**Figure 10**).

### II.2.9.2. Ionones and Damascones

Ionones and damascones are compounds that belong to C<sub>13</sub>-norisoprenoids (norterpenoids), which are carotenoid-derived aroma compounds. The most known representatives are  $\alpha$ - and  $\beta$ -ionone, and  $\alpha$ - and  $\beta$ -damascone that occur in many essential oils (**Figure 10**) [28].



**Figure 10** : Structures of some Irregular Terpenoids.

### III. Pharmacological Activities

#### III.1. Pharmacological Activities of Hemiterpenoids

Isoprene (2-methyl-1,3-butadiene), is the most abundant compound of the group of hemiterpenes produced by plants and is also known as basic unit of all terpenes. Isoprene plays an important role in modulating the biological activity of isoprenoids, and determines their utility as tools to study and treat human diseases. Several reported studies have shown that hemiterpenoids have a wide range of pharmacological activities including anti-inflammatory, antioxidant, hepatoprotective, as shown in **table 2**.

**Table 2:** pharmacological activities of some hemiterpenoids

Compounds	Activities	Sources and references
Cibotiumbaroside B (9)	Suppressed osteoclast formation in a dose-dependent manner and inhibited up to 73 at a 200 $\mu$ M concentration	<i>Cibotium barometz</i> (L.) J. Sm [29]
1-O-caffeoyl-6-O-(4'-hydroxy-2'-me-thylene-butroyl)- $\beta$ -D-glucopyranose (8)	Showed strong inhibitory activity towards NO production and were similar to that of the positive control 1-NMMA (IC <sub>50</sub> = 15.07 $\pm$ 0.86 $\mu$ g/mL)	<i>Spiraea prunifolia</i> leaves [30]
Cibotiumbarosides F (10)	Exhibited remarkable hepatoprotective activity against APAP-induced acute liver damage in vitro. (IC <sub>50</sub> = 10 mM)	<i>Cibotium barometz</i> (L.) J. Sm[29]

#### III.2. Pharmacological Activities of Monoterpenoids

They serve as important chemotaxonomic markers and many are bioactive agents. In a recent study, a group of iridoids were discovered to have anti-hepatitic C virus (HCV) activity. The study found that only the iridoid aglycones such as lamiridosins A/B and genipin were active against HCV, and their corresponding glycosides such as lamalbid and geniposide showed no activity against HCV. Besides, several natural occurring monoterpenes have shown antifungal [30], anticancer [31], antibacterial [32], anti-inflammatory [33], as well as beneficial effects on the cardiovascular system [34].

**Table 3:** Pharmacological activities of some monoterpenoids

Compounds	Activities	Sources and references
Citronellol (26)	Presented antifungal activity on <i>Trichophyton rubrum</i> (MIC: 8–1024 $\mu$ g/mL) and inhibited 50% of the strains tested to 64 $\mu$ g/mL. In the presence of sorbitol, citronellol had an increased MIC for 4096 $\mu$ g/mL.	Essential oil of plants of the genus <i>Cymbopogon</i> [30]
Thymol (27)	Treatment for 24 h of gastric cells with 100, 200, and 400 $\mu$ M of thymol showed anticancer activity against human gastric cancer cells via the inhibition of cell growth and induction of apoptosis	<i>Thymus vulgaris</i> L. [31]
Carvacrol (28)	Significantly reduced the ear edema induced by 12-O-tetradecanoylphorbol acetate and arachidonic acid at 0.1 mg per ear (43% and 33%, respectively), similar to indomethacin at 0.5 mg per ear or 2.0 mg per ear (55% and 57%, respectively)	Essential Oil of Oregano. [33]

#### III.3. Pharmacological Activities of Sesquiterpenoids

Sesquiterpenoids have been reported to possess several pharmacological activities such as antimalarial, cytotoxic, antifungal, hepatoprotective, antibacterial, antiviral, antifeedant, anti-inflammatory, antinociceptive, inhibition of nitric oxide production, antileishmanial, lymphocyte proliferation and hydroxyl radical scavenging. Some of these activities are represent in **table 4**.

**Table 4 :** Biological activities of some sesquiterpenoids.

Compounds	Activities	Sources and references
Tatridin A (51) and Tanachin (52)	Showed significant in vitro antiplasmodial activity against the D10 Plasmodium falciparum strains using the pLDH assay with IC <sub>50</sub> 0.4 $\mu$ M and 0.5 $\mu$ M respectively.	<i>Oncosiphon piluliferum</i> [35]
11 $\beta$ ,13-dihydroveranolide (53) and 11 $\beta$ ,13,17,18-tetrahydroveranolide (54)	These compounds exhibited the strongest antiplasmodial activities (IC <sub>50</sub> values : 1.1–4.8 $\mu$ M) against the chloroquine-sensitive strain PoW and against the chloroquine-resistant clone Dd2 of Plasmodium falciparum.	<i>Vernonia colorata</i> [36]
Laurebiphenyl (40)	It showed moderate cytotoxicity against adenocarcinoma (A549), stomach cancer (BGC-823), hepatoma (Bel 7402), colon cancer (HCT-8), and HELA cell lines, with IC50 values of 1.68, 1.22, 1.91, 1.77 and 1.61 $\mu$ g/mL, respectively	<i>Laurenciatristicha</i> [37]
Polygodial (63)	It had excellent antifungal activity against <i>Saccharomyces cerevisiae</i> (Minimum Inhibitory Concentration (MIC) of 0.78 $\mu$ g/mL), <i>Hansenula anomala</i> , <i>Candida utilis</i> , and <i>Sclerotinia libertiana</i> (MIC of 1.56 $\mu$ g/mL).	<i>Warburgia stuhlmannii</i> and <i>Warburgia ugandensis</i> [38]
Epi-cubenol (60),	It showed significant hepatoprotective, it showed marked reduction in	<i>Juniperus sabina</i>

	the levels of AST, ALT and GGT (41.29, 38.38 and 23.48%) compared with silymarin (50.08, 67.31 and 50.51%).	[39]
Thujasutchin J (58) and (+)-mayurone (59)	Displayed potent inhibitory effect against <i>Staphylococcus aureus</i> (CMCC 26003), methicillin-resistant <i>Staphylococcus aureus</i> (JCS 4744), <i>Bacillus cereus</i> (ATCC 10876), and <i>Staphylococcus epidermidis</i> (ATCC 12228) with MICs ranging from 6.25 to 25 µg/mL.	<i>Thuja sutchuenensis</i> [40]
Artefrenic acid C (47) and G (48)	They exhibited inhibitory effects against LPS-stimulated nitric oxide (NO) production in RAW 264.7 macrophage cells with IC <sub>50</sub> values of 10.8, 12.6, and 11.7 µg/mL, respectively	<i>Artemisia freyniana</i> [41]

### III.4. Pharmacological Activities of diterpenes

This class of compounds showed significant biological activities including anti-inflammatory, antimicrobial, anticancer, and antifungal activities. Some of the diterpenes also have cardiovascular activity, such as grayanotoxin, forskolin, eleganolone, marrubenol, and 14-deoxyandrographolide. Kaurane and pimarane-type diterpenes are also biologically active metabolites isolated from the roots and leaves of different plants (Table 5).

Table 5 : Biological activities of some diterpenoids.

Compounds	Activities	Sources and references
Genkwanine P (77) and laurifolioside A (78)	Compounds 77 and 78 exhibited potential antihepatitis B virus activities with IC <sub>50</sub> 46.5 and 88.3 mg/mL against HBsAg.	<i>Wikstroemia chamaedaphne</i> [42]
Cephinoids H (79)	It demonstrated an inhibition of 49.0% by administration to zebra fish at a dose of 60.0 ng/mL, compared to cisplatin (DDP, 22.4%) at 15.0 µg/mL. It might affect the NF-κB signaling pathway rather than binding to microtubules. Additionally, it showed almost equal anti-inflammatory activities compared to the positive control, MG132.	<i>Cephalotaxus fortunei</i> var. <i>alpina</i> and <i>C. lanceolata</i> [43]
Nudiflopane F (80)	It have strong interactions with the iNOS protein by targeting residues of the active cavities of iNOS in BV-2 cells (IC <sub>50</sub> 28.1 and 23.3 µg/mL).	<i>Callicarpa nudiflora</i> [44]
Drechmerin B (84)	B displayed antimicrobial activity against <i>C. albicans</i> with an MIC value of 12.5 µg/mL.	<i>Endophytic fungus Drechmeria sp.</i> [45]
Eupheliotriol F (82) and L (83)	Eupheliotriol F and L exhibited significant cytotoxicity against MCF-7 and PANC-1 cell lines.	<i>Euphorbia helioscopia</i> [46]

### III.5. Pharmacological Activities of Sesterterpenoids

These types of compounds are biologically active having anti-inflammatory, anticancer, antimicrobial, and antifungal activities (Table 6).

Table 6 : Biological activities of some sesterterpenoids.

Compounds	Activities	Sources and references
Thorectandrol A (92) and B (93)	Compounds 92 and 93 inhibited the growth of MALME-3M (melanoma) and MCF-7 (breast) cancer cell lines in the range 30-40 µg/mL.	Marine sponge <i>Thorectandra sp</i> [47]
Cybastacines A (88) and B (89)	Showed strong activity against clinical isolates of <i>Nocardia</i> spp., <i>M. abscessus</i> , <i>Enterococcus</i> spp., and <i>Staphylococcus</i> spp., with MICs of ≤4 µg/mL.	<i>Nostoc sp.</i> <i>Cyanobacterium</i> [48]
3-anhydro-6-epi-ophiobolin A (101), 8-epi-ophiobolin J (102), and Ophiobolin J (103)	Compounds 101, 102, 103 showed significant inhibitory potency against LPS-induced NO production with IC <sub>50</sub> values in the range of 5.1 ± 0.3 to 20 ± 1 mg/mL.	Fungus <i>Bipolaris sp</i> [49]
Ophiobolin K (87)	Compound 87 showed cytotoxic activity against various tumor cell lines, including adriamycin-resistant mouse leukemia cells (P388), with IC <sub>50</sub> of 0.27 - 0.65 µg/mL.	<i>Emericella varicolor</i> [50]
Ophiobolins B (104)	Ophiobolins B showed antifungal effect on different zygomycetes fungi with MIC values of 3.175 - 50 mg/mL and 25 - 50 mg/mL respectively.	genus <i>Bipolaris</i> [51]

### III.6. Pharmacological Activities of triterpenoids

Several triterpenoids have shown promising biological activities including cytotoxicity [52], cancer chemopreventive [53], anti-HIV [54], and anti-inflammatory [55] activities. Furthermore, triterpenoids are known to possess additional biological activities such as hepatoprotective effect [56], and activity involving the treatment of Alzheimer's disease [57].

Herein, we are discussing some recently published bioactive triterpenes (Table 7).

**Table 7 :** Biological activities of some triterpenoids

Compounds	Activities	Sources and references
Serratenediol (110)	significantly suppressed proliferation of HL-60 cells, with an inhibitory activity of 81.8%, with IC <sub>50</sub> value of 12.9 μM	<i>Lycopodium serratum</i> [58]
Polyporenic acid B (118)	It showed strong cytotoxicity against the HCT116, A549 and HepG2 cell lines with IC <sub>50</sub> values of 8.4, 12.1, and 12.2 μM, respectively.	<i>Fomitopsis palustris</i> [59]
3α,22-diacetoxy-7α-hydroxyl-5α-lanost-8,24E-dien-26-oic acid (111)	showed a remarkable cytotoxic activity against 95D and HeLa human tumor cell lines with IC <sub>50</sub> values of 23.0 and 14.7 μM, respectively	<i>Ganoderma lucidum</i> [60]
Sessiliflorin (112)	anti-HIV-1 activity in the syncytium reduction assay with EC <sub>50</sub> values of less than 8.02–171.61 μM	<i>Gardenia sessiliflora</i> [61]
Cyclocariols A (119), B (120) and H (121)	They were tested against human colon tumor (HCT-116) cell lines, exhibited good activities with IC <sub>50</sub> values of 6.53, 4.94, and 6.48 μg/mL, respectively.	<i>Cyclocarya paliurus</i> [62]
Xuedanencins G (122)	G and H were evaluated for cytotoxic activity against the Hela human cancer cell line and compounds showed significant cytotoxicity with IC <sub>50</sub> value at 1.82 and 2.45 μM, respectively.	<i>Hemsleya penxianensis</i> [63]
Ginsenosides Rh1 (107) and Ginsenosides Rg1 (108)	They showed varying degrees of protection against D-GalN/TNF-α-induced cell death in primary cultured mouse hepatocytes, with IC <sub>50</sub> values of 105 and 111 μg/mL respectively.	<i>Panax vietnamensis</i> [64]
Ursolic (105) and oleanolic acids (106)	They displayed the antibacterial effect, with MIC values ranging from 30 μg/mL to 80 μg/mL against the following microorganisms : Streptococcus mutans, Streptococcus mitis, Streptococcus sanguinis, Streptococcus salivarius, Streptococcus sobrinus, and Enterococcus faecalis	<i>Miconia species</i> [65]

### III.7. Pharmacological Activities of tetraterpenoids

Carotenoids are the most popular tetraterpenoids, and also one of the most powerful nutrients (medicine) on earth due to their potent antioxidant properties [60]. In addition to that, carotenoids exhibit a number of important protective effects in human health including antioxidant, anti-inflammatory, anti-cancer properties, the inhibition of malignant tumor growth, anti-aging, anti-atherosclerosis, and the induction of apoptosis. Several different biological activities related to some tetraterpenoids compounds are listed and briefly described in the table below (Table 8).

**Table 8 :** Biological activities of some tetraterpenoids

Compounds	Activities	Sources and references
Lycopene (124)	inhibited NF-κB signaling pathway through IκB phosphorylation, DNA binding, and p65 translocation ((1–10 μM)	<i>Solanum lycopersicum L.</i> [67]
Lutein (126)	Inhibited nuclear localization of p65 subunits and IκBα protein degradation. In addition, compound 126 also inhibited activation of NF-κB signaling. can protect from oxidative stress and cataract at 100 mg/kg body weight (BW)	fruits, vegetables and egg yolk. [68]
Astaxanthin A (129)	Acted as a safeguard against oxidative damage through different mechanisms.	<i>Haematococcus pluvialis</i> [69]
β-carotene (125)	Acted as a chemotherapeutic agent regulating the invasion and metastasis of neuroblastoma via hypoxia inducible factor-1α (HIF-1α) (20 μM)	(derived from carrots, apricots, mangoes, red pepper, kale, spinach, broccoli)[70]
Canthaxanthin (128)	Inhibited cancer cells proliferation when administrated at a dosage of 6,680 mg/Kg	Natural source [71]
Crocin (127)	Induces apoptosis of MCF-7 cells : activates of caspase-8	<i>Crocus sativus L</i> [72]

### III.8. Pharmacological activities of Irregular Terpenoids

Irregular terpenoids exhibit a broad spectrum of biological activities, such as antiinflammatory and antioxidant activities [73]. Several studies have revealed that these compounds protect organisms against a wide range of diseases. Table 9 exhibits pharmacological activities of main irregular terpenoids against different diseases.

**Table 9 :** Biological activities of some irregular terpenoids

Compounds	Activities	Sources and references
Asperterpenes A (137) and B (138)	Exhibited inhibitory activities against BACE1 with IC <sub>50</sub> values of 0.078 and 0.059 $\mu$ M, respectively	<i>Aspergillus terreus</i> [74]
$\beta$ -ionone (135)	Showed anti-proliferation activity on cancer cell by the MTT assay with IC <sub>50</sub> values from 200 $\mu$ M	Fruits[75]
Spiroapplanatumines G (134)	Compound 134 inhibited JAK3 kinase with IC <sub>50</sub> values of 7.0 $\mu$ M.	<i>Ganoderma applanatum</i> [76]
Amestolkolides B (132)	Exhibited anti-inflammatory activity <i>in vitro</i> by inhibiting nitric oxide (NO) production in lipopolysaccharide activated in RAW264.7 cells with IC <sub>50</sub> values of 30 $\pm$ 1.2 and 1.6 $\pm$ 0.1 $\mu$ M, respectively	<i>Talaromyces amestolkiae</i> YX1 [77]

#### IV. Distribution

Terpenoids are a very diverse group of natural compounds which can be found in a number of plants. Monoterpenoids are chief components of the essential oils and are known for their aromatic properties. These compounds are the major constituents of galbanum (*Ferula gummosa* Boiss.) (80%), *Angelica* species (73%), hyssop (70%), rose (54%), peppermint (45%), juniper (42%), frankincense (40%), spruce (38%), pine (30%), cypress (28%), and myrtle (25%). In general, monoterpene hydrocarbons such as  $\alpha$ - and  $\beta$ -pinene, limonene,  $\Delta^3$ -carene, and myrcene are found as complex mixtures in most essential oils, particularly in those obtained from plant leaves. Flower and seed essential oils tend to have more specialized monoterpenoids present. When the molecule is optically active, the two enantiomers are very often present in different plants: (1)- $\alpha$ -pinene from *Pinus palustris* Mill; (2)- $\beta$ -pinene from *Pinus caribaea* Morelet and *P. pinaster* Aiton; S-(1)-linalool from coriander (*Coriandrum sativum* L.); and R-(2)-linalool from *Cinnamomum camphora* (L.) J. Presl [78].

Iridoids are widely distributed in sympetalous plants within the dicotyledons. The presence of iridoids has been reported in approximately 50 plant families, such as Apocynaceae, Gentianaceae, Loganiaceae, Pedaliaceae, Plantaginaceae, Rubiaceae, and Scrophulariaceae [79].

Most of the sesquiterpenoids (especially hydrocarbons), as monoterpenoids, are considered to be essential oil components, since they belong to the steam distillable fraction often containing the characteristic odoriferous components of the plant [80]. Sesquiterpenoids are the principal constituents of cedarwood (98%), vetiver (97%), spikenard (*Nardostachys jatamansi* (D. Dan) DC) (93%), sandalwood (90%), patchouli (71%), myrrh (62%), and ginger (59%). Sesquiterpene lactones are a group of secondary metabolites found across the plant kingdom being most common in families such as Cactaceae, Solanaceae, Araceae, and the Euphorbiaceae. However, they are most prevalent in the Asteraceae, where they can be found almost ubiquitously [81].

Mono, di and sesqui-terpenoids are of very limited distribution. The universally distributed diterpenes are gibberellic acid and phytol. The first one is a plant hormone and the second the side chain of chlorophyll-a [82]. Diterpenoids are of fungal or plant origin and are found in resins, gummy exudates, and in the resinous high-boiling fractions remaining after distillation of essential oils.

Sesterterpenoids are a relatively small group of terpenoids, but their sources are widespread. They have been isolated from terrestrial fungi, lichens, higher plants, insects, and various marine organisms, especially sponges. The structural conciseness and diverse bioactivity of sesterterpenoids have made them attractive targets for both biomedical and synthetic purposes [83,84].

Triterpenes are known to be of widespread distribution. This is true of the pentacyclic triterpenoids  $\alpha$ - and  $\beta$ -amyrin and the derived acids, ursolic and oleanolic acids. These and related compounds occur especially in the waxy coatings of leaves and on fruits such as apple and pear. Triterpenoids are also found in resins and barks of trees and in latex. Certain triterpenoids are notable for their palate properties, particularly their bitterness. The most characteristic example is limonin, the bitter principle of Citrus fruits. This compound belongs to a series of pentacyclic triterpenes known as limonoids and quasinoids. They occur principally in the Rutaceae, Meliaceae, and Simarubaceae [84]. Carotenoids (tetraterpenoids) present in plants have two principal functions : as accessory pigments in photosynthesis and as coloring agents in flowers and fruits. In flowers (daffodil, pansy, marigold), they mostly appear as yellow colors, while in fruits they may also be orange or red (rose hip, tomato, paprika) [84].

Polyterpenoids can be found in rubber and occur as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*, Euphorbiaceae). Especially rich in latex are the families of Moraceae, Apocynaceae, Euphorbiaceae, Papaveraceae, and Asteraceae. Rubber is absent in monocotyledons, gymnosperms, and lower plants.

## V. Conclusion

Among plant secondary metabolites, terpenoids are the most abundant and diverse class. Terpenoids are commonly present in higher plants, and normally produced in vegetative tissues, flowers, and, occasionally, roots. The diversity of terpenoids is probably a reflection of their many biological activities in nature, which have made them a widely used resource for traditional and modern human exploitation. Naturally occurring terpenoids provide new opportunities to discover new drugs with minimum side effects. They are usually the constituents of essential oils of economic importance as flavors and perfumes. These are also commonly used as natural flavoring compounds in food industries.

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