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Research Paper

Extraction, Isolation and Biosynthetic Scheme of Terpenoids and its Pharmaceutical Activities in Drug Designing and Development

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Abstract

A large number of biological and pharmacological effects can be attributed to a class of naturally occurring compounds called terpenoids, also known as terpenes. These methods have shown promise in treating a wide range of infectious disorders, from bacteria and fungi to inflammation and even cancer. Terpenoids are built from two separate five-carbon-atom "backbones" in their most basic form. Monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), and sesterterpenes (C25) are only a few examples of the various terpenoid classes that may be broken down by the number of carbon atoms in their carbon skeletons. Synthesis may take place either chemically or biologically, and both methods can be employed to manufacture terpenoids. Drugs generated from terpenoids may be synthesised using a number of chemical routes; these routes are all now serving vital roles in modern medicine. This review will cover the multiple medicinal benefits of terpenoids, as well as their extraction and separation, structural elucidation, biosynthesis, chemical synthesis, and biosynthesis.

Introduction

The diagnosis, treatment, and prevention of illness all rely heavily on natural products, a sizable subset of organic chemicals (Newman et al., 2000). More than seventy percent of the chemotherapeutic drugs that are used to treat infectious and malignant illnesses are created and extracted from a range of plants (Newman et al., 2023). These medicines are utilised in the present day all around the world. Terpenes are important class of natural products with 23,000 known compounds and are considered as largest class of natural products. Terpenoids are a group of compounds that are widely used as flavourings, spices, and scents in several consumer products, including food and personal care items. Multiple terpenoids are employed as bioactive components in the process of generating novel drugs and producing new therapeutic formulations. Antimalarial and anticancer terpenoids include artemisinin and paclitaxel, respectively. Additionally. Marine-sourced terpenes have shown promising medical use. One example is eleutherobin, which was isolated from the Australian coral *Eleutherobia sp.* (Lindel et al., 1997), and another is sarcodictyin, which was isolated from the stoloniferan coral *Sarcodictyon roseum* (D'Ambrosio et al., 1997; D'Ambrosio et al., 1998). These compounds are very effective in killing a wide variety of tumour cells. The important relevance of diverse terpenoids as preventive and therapeutic agents in numerous medical fields is explored in this review article, which focuses on several different forms of terpenoids, including monoterpenes, sesquiterpenes, diterpenes, and sesterterpene.

Extraction and Isolation

Terpenoids are extracted as a complex combination utilising a broad variety of extraction procedures, and their origins span the plant kingdom. There are a wide range of possible settings for this operation. Information on how to do these steps may be found online. Low combination terpenes, such as monoterpenes and sesquiterpenes, are extracted from plants using steam distillation. For this purpose, the plant material is heated to a high enough temperature to provide the desired effect. In this process, the plant matter is heated to a high temperature, and then steam is passed through the substance and the expected outcome occurs because of this. The most common methods for obtaining terpenes from plants include liquid/liquid partitioning, which starts with an alcoholic or acetic extract, and serial solvent extraction, which relies on the increasing polarity of the solvents utilised. These two methods are similar in that they both rely on the polarity of the solvents increasing over time during the extraction process. It is believed that the polarity of the solvents employed in any of these procedures increases with time as extraction progresses. After the plants have been dried, they are finely ground, the liquid is extracted using the Soxhlet device, and finally the liquid is allowed to soak at room temperature. All of these precautions are taken to eliminate the risk of contamination, of any kind, including that which may originate from artefacts. To be able to identify and characterise the various terpenoids, it is necessary to first isolate the pure chemicals and then prepare them for spectroscopic study. After terpenoids are

properly identified, the requisite biological processes to produce them may begin, and studies on their potential use in pharmaceuticals can be undertaken. There are likely to be a number of steps involved in isolating pure terpenoids from their extract, making the process not only time-consuming but also costly. Minutes were the unit of measure for the sum in a small number of other contexts. Separating pure terpenoids is often accomplished using many chromatographic techniques (Hostettmann et al., 1998). These methods include preparative high-performance liquid chromatography, column chromatography, and radial chromatography. High-performance liquid chromatography and gas chromatography with mass spectrometry may be used to isolate structurally closed combinations of complex terpenoids, often known as essential oils. The extraction process can be summarized in the following figure 1.

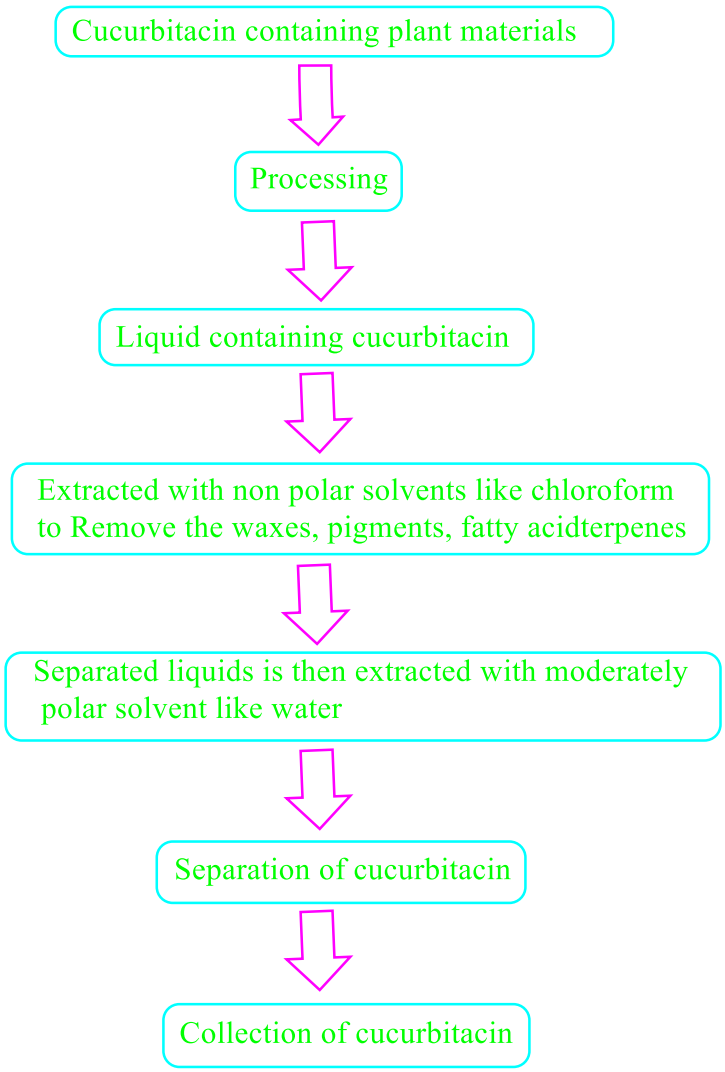

Fig 1: General schematic diagram of terpenoid extraction

Structure Elucidation

In order to learn more about the structures of terpenoids, scientists use a wide range of spectroscopic and chemical methods to examine the compounds once they have been separated and purified. But

nowadays the only spectroscopic methods are used for the determination of structure of the very small amounts of extracts. The availability of powerful nuclear magnetic resonance (NMR) techniques for the elucidation of the newly and previously known extracted terpenoid is an easy task, and their structures can be easily identified. Different NMR studies are helpful for the elucidation of terpenoids are ^{1}H, ^{13}C and 2D NMR including stereochemical chiral centres identifications of different compounds. The crystal structure of solid crystalline terpenoids may also be determined by X-ray diffraction investigation. Some terpenoids can be synthesized in both enantiomeric forms having more than one chiral centre, except for triterpenoids biosynthetically by living organism. The absolute configuration of different terpenes is determined through various mechanism that is helpful for the study of biological applications. Various absolute configuration applications such as enzymatic reactions, chiroptical data, X-ray analysis, exaction chirality, NMR techniques and circular dichroism processes are used for the determination of terpenoids structured respectively (Crabbé, 2012; Harada et al., 1983; Eliel et al., 1994).

Biosynthetic Scheme

Lots of different structural and chemical configurations of terpenoids are described in the literature. Building blocks for terpenoids include the electrophilic isomers isopentenyl diphosphate and dimethylallyl diphosphate. In the scientific literature, two distinct but related pathways are proposed as potential means of terpenoids' production. Linear prenyl diphosphates cannot be synthesised without the enzymes known as prenyl transferases. To begin the biosynthesis of terpenoids, these are required. In the presence of enzymes that catalyse prenyltransferases, biosynthesis starts with the sequential head-to-tail condensation of an isoprene unit (IPP) and a prenyl diphosphate or DMAPP (Fig 1). This reaction converts allylic diphosphate into allylic cation instead of returning the diphosphate ions that were previously present. As this cation keeps hammering away at the IPP molecule, more C-C and C=C bonds are formed (Ogura et al., 1998) through the stereospecific elimination of protons. When an enzyme called prenyltransferase is present, a series of products with controlled lengths and stereochemistry may be generated by sequentially condensing allylic prenyl diphosphate with isopentenyl pyrophosphate. From ten carbon atoms (in the case of geranyl diphosphate, GPP, C10) to millions of carbon atoms (in the case of natural rubber), the chain length of prenyl diphosphates may vary widely (Wang et al., 2000). Prenyltransferases are enzymes responsible for a catalytic pathway that requires the divalent metal ions Mg^{2+} and Mn^{2+}.The condensation of DMAPP and IPP in the presence of farnesyl diphosphate (FPP, C15) synthase and GPP synthase enzymes synthesized a precursor to FPP, monoterpenes and sesquiterpenes respectively. The enzymes farnesylgeranyl diphospate (FGPP, C25) synthase and geranylgeranyl diphosphate (GGPP, C20) synthase are both involved in the synthesis of FGPP precursors, including diterpene and sesterterpene, via the same condensation process (Tachibana et al., 1994). The cyclization of linear prenyl diphosphates mediated

by terpenoid class (called as isoprenoid synthases) in the presence of catalyst synthesizing various terpenes (Caruthers et al., 2000).

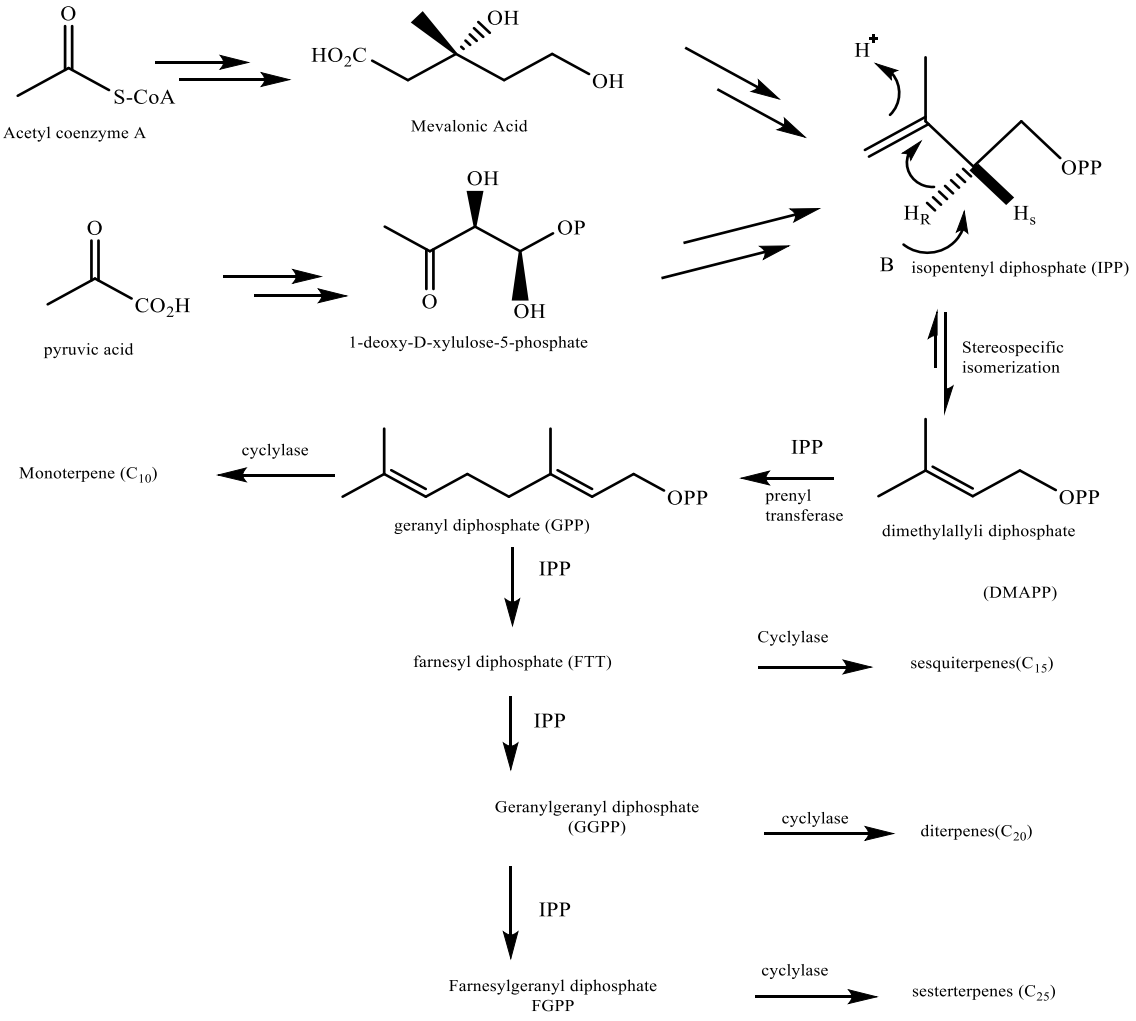

Fig 2: Pathway for synthesis of terpenes

Terpenes with specific stereochemistry may be rearranged and cyclized with the help of enzymes known as cyclase (Rising et al., 2000). To facilitate chemical bonding, substrate carbon undergoes a change in hybridization. Isoprene unit cyclization processes, repetitions, and rearrangements are important for studying the structure and chemistry of different terpenoids. GPP's rearranging and cyclizing led to the formation of a plethora of mono- and bi-cyclic terpenes; FGPP, FPP, and GGPP's larger precursors led to the formation of a greater variety of terpene carbon skeletons. Terpenes' cyclic and linear skeletons may be joined in many ways to provide structural diversity. A wide range of terpenes with oxidised carbon chains and carbocyclic ring structures exhibit carbonyl and alcohol functionality. Moreover, numerous terpenoids' sugar moieties may be found in their skeletons. Polycyclic and bicyclic ring structures consisting of three to four members are prominent in terpenes (Wagner et al., 2003). To conclude that, prenyl diphosphate based on five carbon isoprene unit, are further classified as C5

hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), and triterpenes (C30) respectively.

Terpenoid Chemical Synthesis and their Development in Drug Production

The total synthesis (Nicolaou et al., 1996) method was developed in the early 20th century to isolate and verify the active ingredient in a natural extract. In any case, developments in analytical instruments and purifying procedures have made it simple to find the structure explicitly. However, full synthesis remains the gold standard for evaluating the absolute and relative stereochemistry of complex natural product molecules. The large-scale production of terpenoids with complex structures is possible by total synthesis, which makes use of commercially available components. The terpenoids participate in a wide range of biological activities. Instead, semi-synthesis is an essential step in the development of medications derived from terpenoids. Isolated paclitaxel is not of adequate amount for human trials (Kingston et al., 2002). Disturbing environmental issues are raised by the needless chopping down of yew trees for use in walling off compounds. The four-step semisynthesis of pacilitaxel from 10-deacetylbaccatin III considerably accelerated the development of Taxol. Needles from a yew tree tested positive for 10-deacetylbaccatin III. As with the T. *beccata*, the yew tree is native to India. Without negatively impacting the tree population, baccatin III or 10-deactyl baccatin III, precursors of paclitaxel, may be harvested and extracted from yew plant needles. Docetaxel, a drug with similar effects to paclitaxel, was mass-produced by semisynthesis. Docetaxel, which is used to treat ovarian and breast cancer (Rowinsky et al., 1997), is more water-soluble than paclitaxel. Semi-synthesis is also involved in the synthesis of artemisinin (Qinghaosu). Artemisinin yields are low (0.5–0.2%) since few genotypes of Annula have the ability to generate yields of more than 1%. Qinghao acid (artemisinic acid, typically 0.2–0.8%) is the most common sesquiterpene found in plants. Converting artemisinic acid to artemisinin is a simple process (seen in Fig. 2) (Jung et al., 1986). In theory, artemisinin can be broken down into lactol. The semisynthetic production of artemisinin analogues, including artemether and the sodium salts of artelinic acid and artesunic acid, which are water-soluble and exhibit antimalarial effect, is possible (Luo et al., 1987). Total synthesis may have a relatively little impact on the production of terpenoid pharmaceuticals, but it is undeniably essential to the growth and development of chemicals that are derived from terpenoids and other natural substances. It is worth noting that a similar approach has been used to reveal the active moiety of Artemisinin, paclitaxel, sarcodictyn A, and eleutherobin (Cinel et al., 2000; Gueritte et al., 2001).

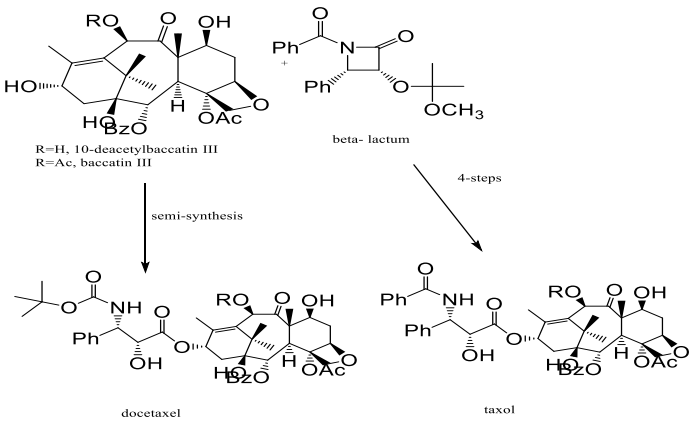

Fig 3: Chemical Synthesis of terpenoids

Pharmaceutical Terpenoids

The scientific literature reports that terpenoids have several therapeutic applications. Researching all biologically active terpenoids compounds would be challenging. Inflammatory, bacterial, malarial, neoplastic, and viral illnesses are only few of the topics covered in the present review articles that investigate the many biological and pharmacological properties of terpenoids. In this chapter, we will quickly go over the many types of terpenoids and their medicinal applications in the pharmaceutical industry.

Monoterpenes

A terpene with just two isoprene unit molecules is called a monoterpene. There are two possible shapes for these monoterpenes: linear and ring-shaped (shown in fig. 3). Terpenoids are the name given to monoterpenes that include oxygen functional groups. Aromatic plant defence resins and flower oils often contain them in high concentrations (Loza et al., 1999). Cherry, herbs, citrus fruits, citrus essential oils, and mint are all examples of fruits that contain monoterpenes that are harmful to humans. When geranyl diphosphate is combined with terpene cyclises (enzymes that speed up the process), a variety of monoterpenes are created (Davis et al., 2000). Many different nutritional monoterpenes have anticancer activity, demonstrating not only the ability to avert cancer's development but also the capability to deteriorate already-formed malignant tumours (Crowell et al., 1999). There are several different trees and plants that contain limonene in large quantities. This limonene comes from citrus fruits and orange peel oil. Because its molecular structure is so similar to that of pharmacological drugs, limonene is of great interest to chemists and biologists. Lemonene has been shown to be effective against cancer cells in both preventative and therapeutic settings. In particular, the monoterpene carvone, which may be found in caraway seed oil, has been shown to be effective in the treatment of lung and forestomach malignancies (Wattenberg et al., 1989). The chemo-preventive effects of carveol against rat mammary cancer are most evident in the drug's early-stage use. The hydroxylated form of limonene, known as perillyl alcohol, has shown promise in the treatment of liver and pancreatic cancers,

especially in rats and hamsters. The chemotherapeutic effect of limonene and its derivatives is investigated experimentally. The red algae *Portieria hornemnnii* is the source of halomin, an acyclic halogenated monoterpene with a unique mechanism of action against lung, kidney, and brain tumour cells (Egorin et al., 1997).

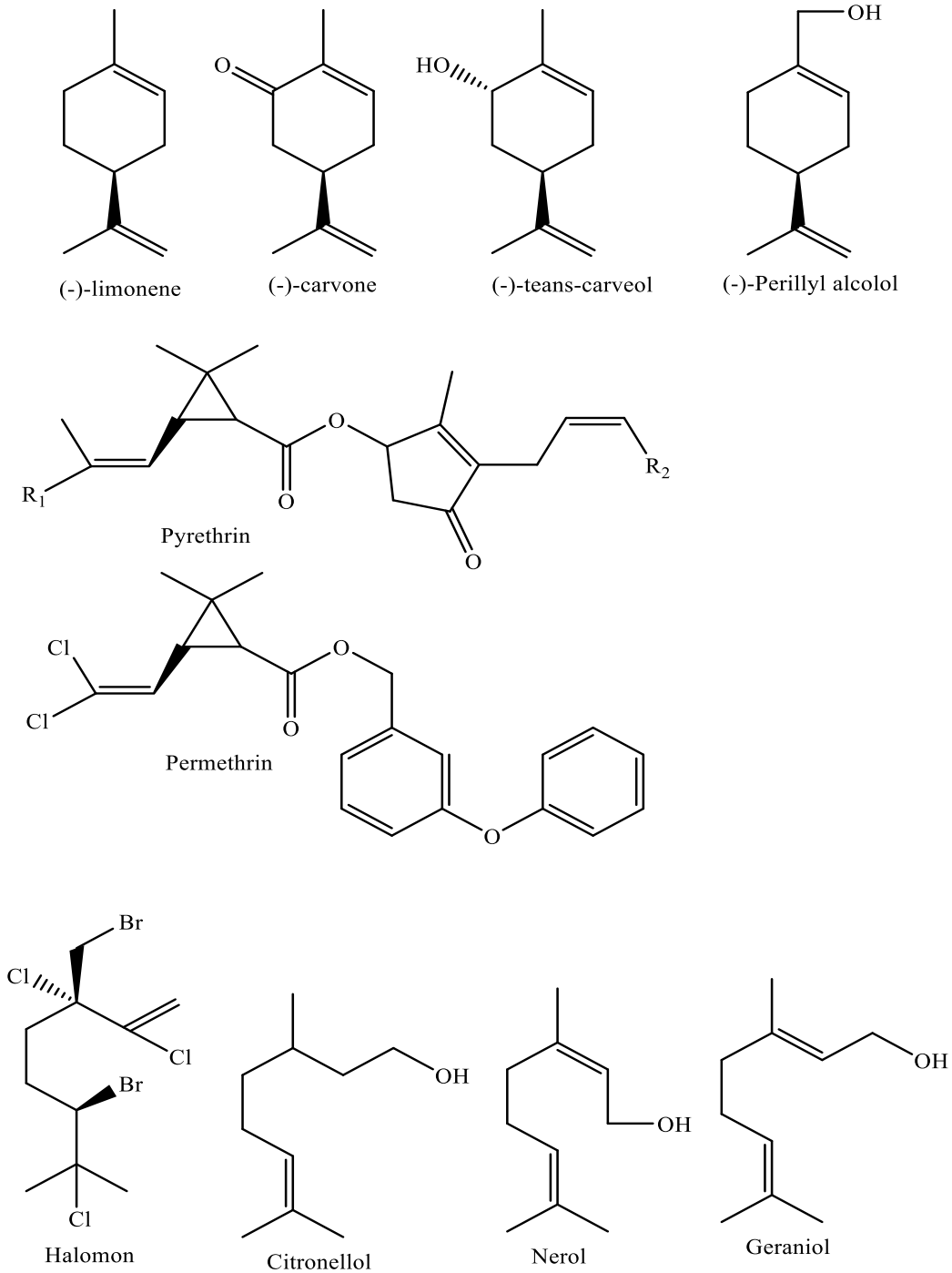

Fig 1: Structure of monoterpenes

Sesquiterpenes

Sesquiterpenes are a kind of terpene that include three isoprene units and, depending on their structure, may be acyclic (shown in fig. 4). Naturally, sesquiterpenes have lower flammability. Sesquiterpene lactones are widely spread (Abraham et al., 2001), have a significant biological role, and are present in both land and sea species. Because of their powerful anti-inflammatory characteristics, these sesquiterpene lactones are often used to treat menstrual problems, gastrointestinal distress, high body temperature, and painful or uncomfortable headaches. Nowadays, those with psoriasis, asthma, and migraines all use them (Williams et al., 1999). Numerous plant species, such as Pyrethrum parthenium, Leucanthemum parthenium, and Tanacetum parthenium, contain the sesquiterpene lactone parthenolide, which has a variety of therapeutic uses. Artemisinin (family Asteraceae), for instance, is extracted from Artemisia annua "Qinghao" and possesses an endoperoxide bridge that is crucial for the treatment of antimalarial illnesses (Brossi et al., 1988). About two hundred years ago, these plants were employed as medicine in China; now, they are used globally as an antimalarial remedy. The malaria-causing Plasmodium falciparum strain is eradicated. Another kind of sesquiterpene is chamazulene. In particular, the antifungal, anti-inflammatory, and antibacterial effects of bisabiolol oxides (A, B), -Bisabolol isolated from Matricaria chamomilla, are quite noteworthy. In contrast to its anti-inflammatory effects, chamazulene unit may suppress the formation of leukotrienes (Safayhi et al., 1994). Approximately 50 sesquiterpenes isolated from herbal plants are used to control M. tuberculosis and tuberculosis (TB), which infect roughly 2 million individuals yearly throughout the world. Similar to guaianolide, germacranolide, and eudesmanolide, sesquiterpene lactones have been shown to effectively combat the TB virus. Another cyano-sesquiterpene with potential for helping M. tuberculosis recover is axisonitrile-3 sesquiterpene, which was discovered in the sponge Acanthella klethra. Furthermore, researchers are interested in puupehenone and its derivatives 15--cyanopuupehenol and 15-cyanopuupehenone (Zjawiony et al., 1998) because to their immunomodulatory, cytotoxic, M. tuberculosis, and antibacterial inhibitory activities. Avarone and avarol belong to a family of marine sesquiterpene lactones that have potent anti-infectious disease action, particularly against HIV. Moreover, reverse transcriptase has been purified from the red sea sponge Dysidea cinerea. To prevent tumour cells from regenerating, nano and pico doses of the sesquiterpene illudin are utilised in therapy. That may invade cancer cells and take over their DNA synthesis is irofulven (Woynarowski et al., 1997). Irofulven sesquiterpene is an antitumor agent because it works by killing off abnormal tumour cells in much the same way as anticancer drugs do. illudins and irofulven are considered useful therapeutic medicines because of their anticancer properties (Jaspers et al., 2002).

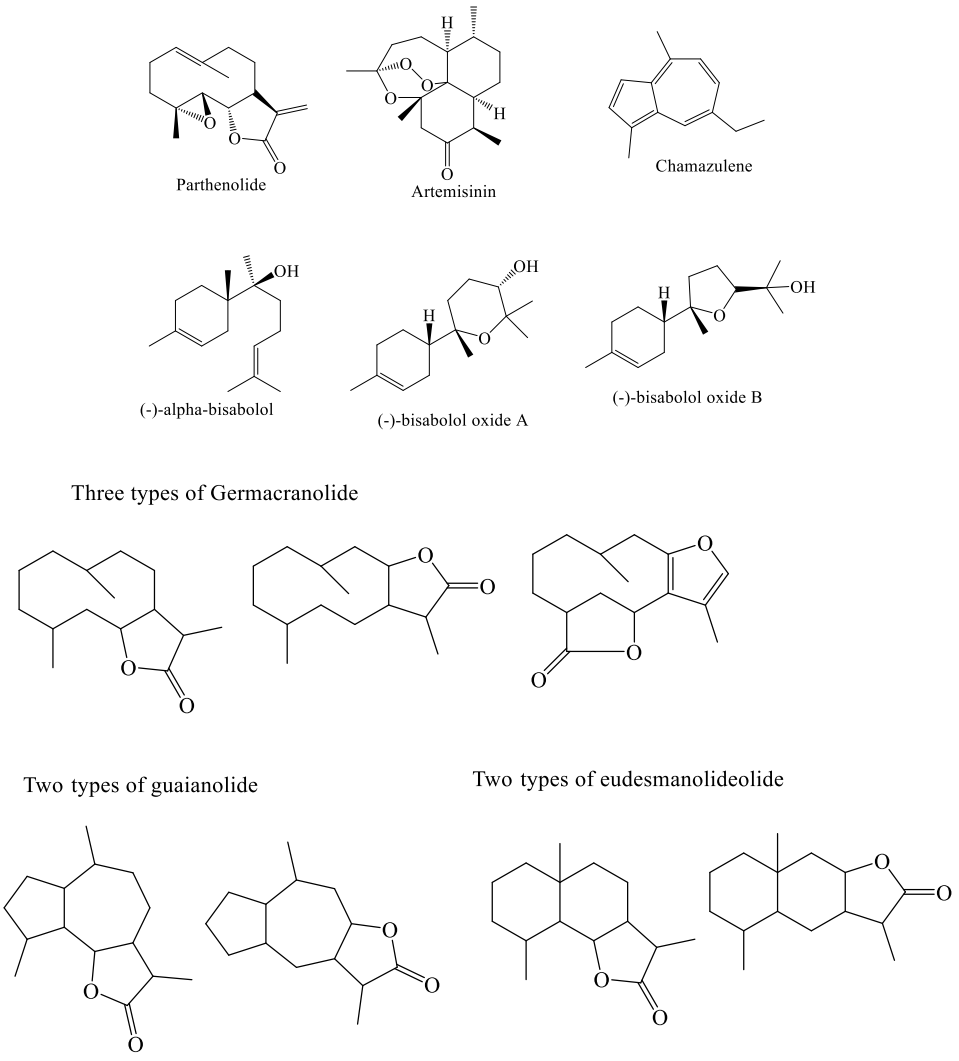

Fig 2: Structure of sesquiterpenes

Diterpenes

Terpenoids such as diterpenes are crucial because of their many medical applications. Like other terpenoids, they have a wide range of species of origin. The reduction of geranylgeraniol yields phytol (Figure 5), one of the most important and easy examples (see also (Rontani et al., 2003). Lucas volkensii is a plant species that is used to get the antituberculosis-property-containing (*E*)-phytol. The ester chain and four-membered oxeane ring in the cancer drug taxol (paclitaxel) (Fig. 5) are responsible for its anticancer effects (Fig. 5). In addition to its use in combating ovarian and lung infections, breast cancer may also be treated with taxol. It is part of today's standard chemotherapeutic armament, used against a variety of cancers (Radjasa et al., 2011). Breast and ovarian cancer patients have had access to paclitaxel since the 1990s, when the FDA first approved it for treatment. Peripheral neuropathy, hypersensitivity, neutropenia, and alopecia are some of the negative effects of paclitaxel. Diterpene glycosides, or pseudo-pterosins, are potent inhibitors of PLA2 with anti-inflammatory and pain-relieving properties (Groweiss et al., 1988). A derivative of pseudopterosin, methopterosin has anti-

inflammatory and wound-healing properties. Similarly, Sphaerococcus coronopifolius is the source of the bromo-diterpene sphaerococcenol A, a diterpene having antimalarial action in different Plasmodium falciparum strains at different stages (Fig. 5). Medications containing chloroquine are often used to treat malaria. Herpesvirus, maryland virus, ann arbor virus, and poliovirus III are only some of the viruses that are neutralised by diterpenes (Giannini et al., 2001).

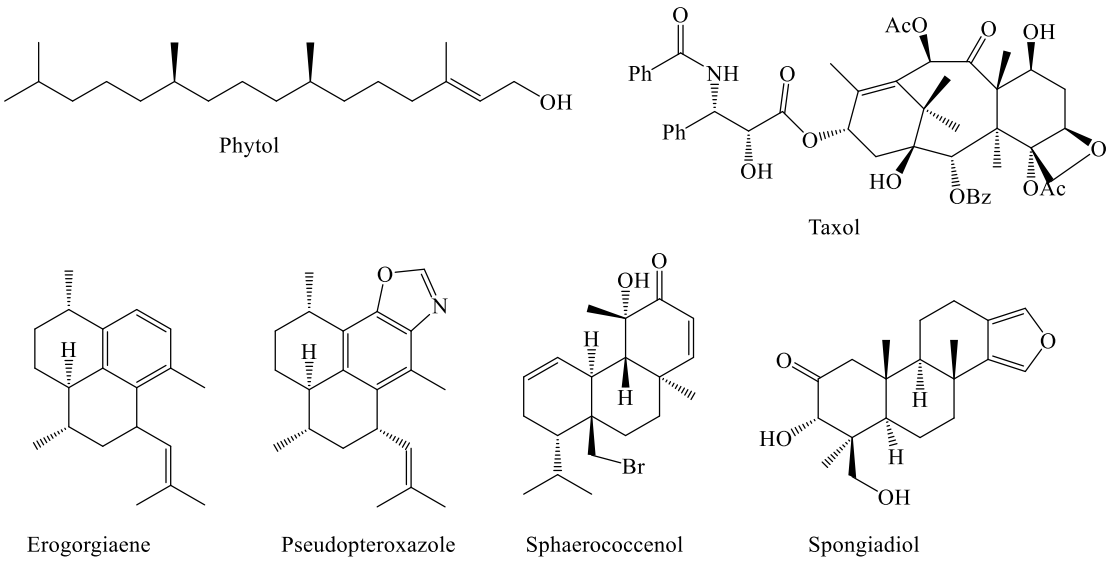

Fig 3: Structure of some diterpenes

Sesterterpene

It is the least common group of terpenoids. The structurally different types of sesterterpene are extracted mostly from marine organism (Shown in Fig. 6) and various species of fungi. Sesterterpene inhabit various biological and pharmacological activities such as inflammatory, phospholipase A2 (PLA2), arachidonic acid production, leukotrienes and prostaglandins. PLA2 are extracted from species sponge i.e., *Cacospongia mollior* which were named after the scalaradial which were used in anti-inflammatory drugs synthesis and their developmental phases (De Silva et al., 1980). Those sesterterpene of marine origin consist of γ-hydroxybutenolide moiety are extensively for the treatment of γ matory and anti-inflammatory activities. The very first moiety of PLA2 sesterterpene are manoalide, extracted from *Luffariella variabilis* of sponge familyshowing significant potency against anti-inflammatory and analgesic activities (Youssef et al., 2002). Similarly, there are various manoalide have been isolated such as petrosaspongiolides M-R, cacospongionolides, luffariellins and luffariellolide. These are act as PLAS2 irreversible inhibitors zone. Among all these compounds petrosaspongiolide M showing great potency against PLA2 inhibitory zone and it also reduced the leucotriene B4, tumor necrosis, prostaglandin E2 level with showing no such type of side effects. Moreover, scalaranestype and salmahyrtisol A novel sesterterpene are extracted from *Hyrtios erecta* of species sponge commonly found in red sea are showing greater potency against human colon carcinoma, human lung carcinoma and murine leukaemia (Renner et al., 2000). Similarly, ophiobolane sesterterpene extracted out from

marine organism such as fungus species i.e., *Halorosellinia oceanica* showed good results against malarial disease. Last but not the least, a group of Mangicols A-G ter-terpenes, extract out from *Fusarium heterosporum* of fungus family having novel compounds of spiro-tricyclic nature.

The occurrence of these terpenoids is the least common of all. Marine creatures (shown in Figure 6) and various types of fungi are the primary sources of the many structurally different types of sesterterpene. Several biological and pharmacological processes rely on sesterterpene, including inflammation, phospholipase A2 (PLA2), arachidonic acid production, leukotrienes, and prostaglandins. *Cacospongia mollior*, a kind of sponge, is the source of PLA2, a scalaradial used in the production of anti-inflammatory drugs and their intermediates (De Silva et al., 1980). There is a lot of interest in marine sesterterpene with the γ-hydroxybutenolide moiety because of its potential anti-inflammatory and anti-microbial effects. Manoalide, which is extracted from the sponge *luffariella variabilis*, serves as the primary component of PLA2 sesterterpene [40]. It has potent anti-inflammatory and analgesic properties. Petrosaspongiolides M-R, cacospongionolides, luffariellins, and luffariellolide are all examples of similar manoalides that have been isolated. These areas function as permanent PLAS2 inhibitors. Petrosaspongiolide M was the most efficient of these drugs in inhibiting PLA2 inhibitory zone formation; it also reduced leucotriene B4, tumour necrosis factor, and prostaglandin E2 levels without generating any side effects. On top of that, scalaranestype and salmohyrtisol against human colon cancer, human lung carcinoma, and murine leukaemia, a novel sesterterpene isolated from the red sea sponge species *Hyrtios erecta* shows increased action (Renner et al., 2000). Similar effectiveness against malarial sickness has been shown by ophiobolane sesterterpene isolated from marine organisms like the fungus *Halorosellinia oceanica*. Finally, a group of ter-terpenes called Mangicols A-G, which were isolated from the *fusarium heterosporum* fungus and feature distinctive spiro-tricyclic chemistry.

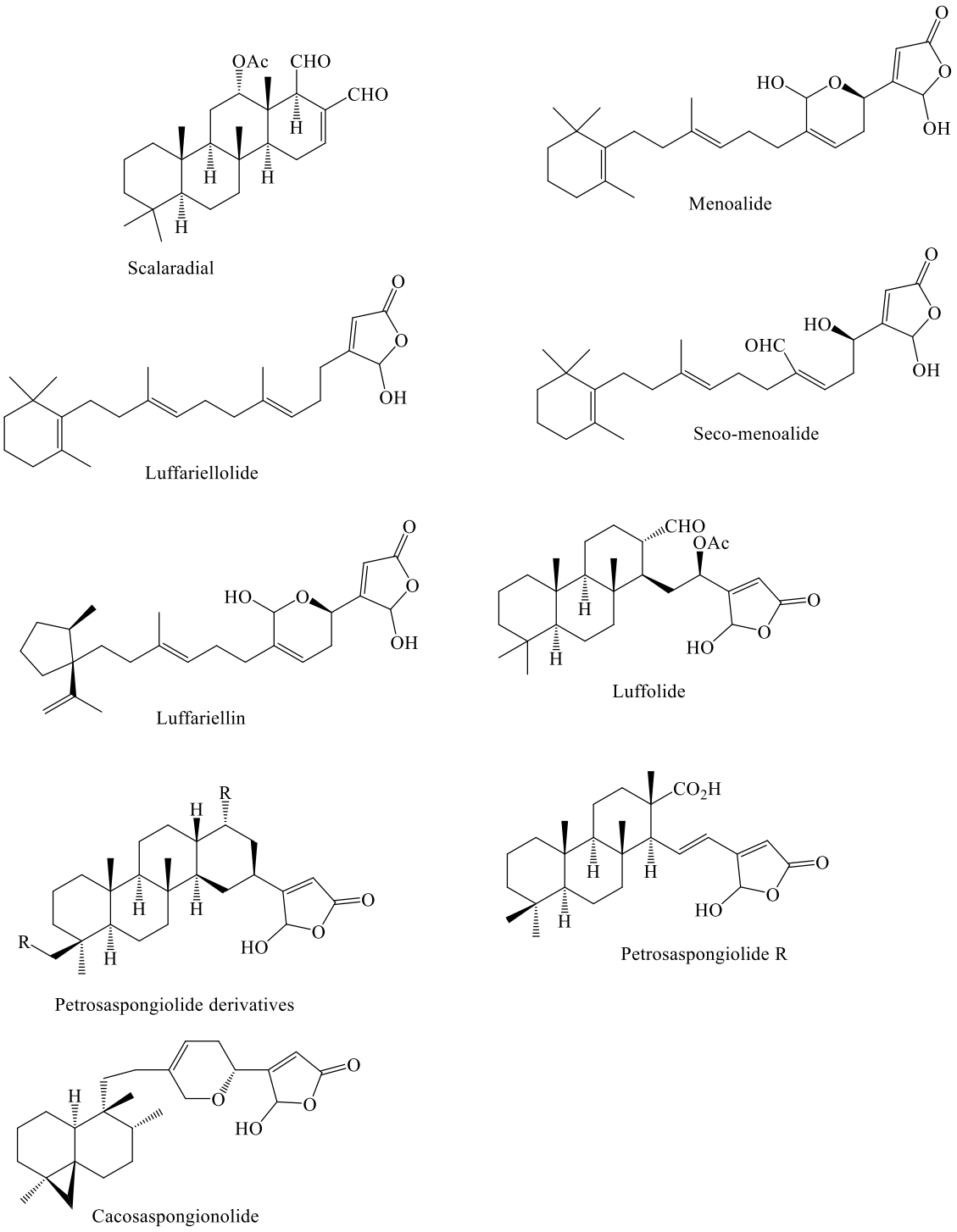

Fig 4: Structure of some sesterterpene

Conclusion

Given the above analysis, it should come as no surprise that the vast majority of the chemicals utilised to treat different illnesses today are derived from natural herbs and plants. This is because nature provides an infinite supply of substances that may be used to cure a wide range of illnesses. The same regulations apply to terpenoids. Even though terpenoids play a key part in the medicinal field for the

drug designing and drug development, it is still unknown, based on the study that has been done so far, what numerous functions terpenoids may play and what impact it may have on growing and spreading their reach in the pharmaceutical industry. Because of this, one can deduce that studying the mechanisms through which terpenoids function in medicine has great promise for future investigation of the drug designing and drug development.

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