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3

Synthesis, and Medicinal Uses of Diterpenoids

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3.1 Introduction

Diterpenes are hydrocarbons with molecular formula $C_{20}H_{32}$. Diterpenoids represent a large and structurally diverse class of compounds derived from four isoprene units linked in a head-tail fashion. According to the number of rings present in diterpenes, these are broadly categorized into phytane, cembrene, labdane, abietane, pimarane, clerodane, and stemarene diterpenoids (Table 3.1). Diterpenes are also classified into different types such as linear or acyclic (Phytol), bicyclic (Sclareol, *Salvia sclarea*), tricyclic (Abietic acid, *Pinus sylvestris*), tetracyclic (tigliane), pentacyclic (Cafestol), and macrocyclic (Taxol, *Taxus brevifolia*) depending on the presence of their skeletal core. These compounds are mainly present in polyoxygenated form with hydroxyl (–OH) and keto (C=O) groups in nature [1].

TABLE 3.1

Classification of Diterpenes

Types of Diterpenes	Number of Rings	Examples of Diterpenes
Acyclic	0	Phytane (Phytol)
Monocyclic	1	Cembrene-A
Bicyclic	2	Sclarene, Labdane
Tricyclic	3	Abietane (abietic acid), Taxadiene (Taxol)
Tetracyclic	4	Stemarene, Stemodene

The molecular structure of diterpenes contains skeletons with 20 carbon atoms (C_{20}). It may be categorized into acyclic: phytane, bicyclic: labdane and clerodane, tricyclic: abietane, pimarane and cassane, tetracyclic: gibberellane, kaurane and

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phytane, bicyclic: labdane and clerodane, tricyclic: abietane, pimarane and cassane, tetracyclic: gibberellane, kaurane and vouacapane, macrocyclic: lathyrane and taxane (Figure 3.1).

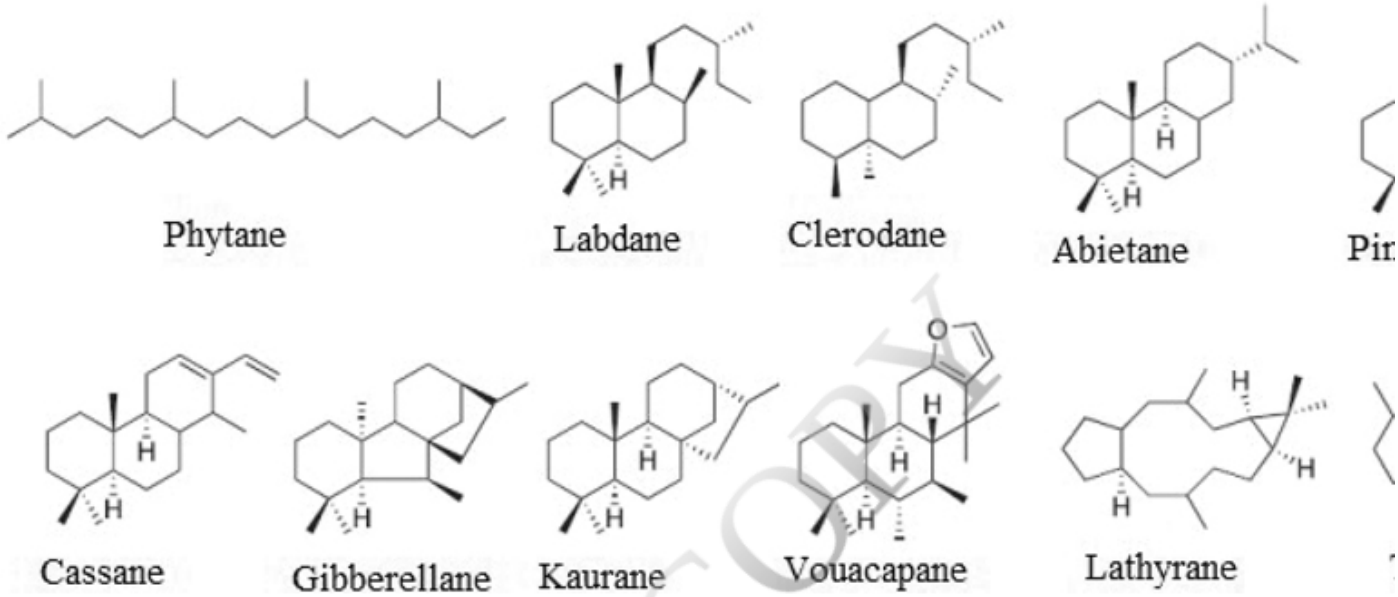

FIGURE 3.1 Molecular structure of diterpenes.

Several diterpenes are produced in plants, animals, cyanobacteria, and fungi via the HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase pathway, mevalonate, or deoxyxylulose phosphate pathways in which geranylgeranyl pyrophosphate act as a primary intermediate. So, diterpenes are derived by the addition of one IPP unit with FPP to produce geranylgeranyl-pyrophosphate (GGPP). From GGPP, structurally diverse terpenoids are generated primarily by two classes of enzymes such as diterpene synthases and cytocromes P450 (CYPs). GGPP is the precursor for the synthesis of the phytane by the action of the enzyme geranylgeranyl reductase [2].

The evaluation of biological activities by *in-vitro* cell-based assays and *in-vivo* animal studies indicates the medicinal effects of diterpenes against a variety of diseases. Diterpenes possess various pharmacological activities including anti-inflammatory, antidiabetic, antihyperlipidemic, anticancer,

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