Labdanes of Natural Origin-Biological Activities (1981-2004)

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Abstract: Terpenoids is a class of natural compounds found in higher plants, mosses, liverworts, algae and lichens, as well as in insects, microbes or marine organisms. Through centuries many of these compounds have been used as ingredients of perfumes, drugs, narcotics or pigments. Labdanes, belonging to the bicyclic diterpenoids group, have been found as secondary metabolites in tissues of fungi, insects, marine organisms, and in essential oils, resins and tissues of higher plants. The diterpenes of labdane type, have been reported to have broad spectrum of biological activities. In this study, the reported bioactivities and/or uses of them, the last two decades (1981-2004), are selected as an attempt to underline their role in nature.

Keywords: Labdane-type diterpenes, plant families, bioactivities.

INTRODUCTION

Terpenoids

Classification of Terpenoids

The widespread numerous class of natural products that are derived from a common biosynthetic pathway based on mevalonate as parent, are named terpenoids, terpenes or isoprenoids with the subgroup of steroids among them as a class.

These compounds are found in higher plants, mosses, liverworts, algae and lichens, as well as in insects, microbes or marine organisms. Steroids can be found in Animal and Plant Kingdoms and in microorganisms. Through centuries many of these compounds have been used as ingredients of perfumes, drugs, narcotics or pigments [1, 2]. The terpenoids are built up of C5 units and the main classes together with the parents of each are gathered in (Table **1**).

Table 1.

C_n	Name	Parent	Subclass	Occurrence
10	Monoterpenoids	GPP	Iridoids	Oils
15	Sesquiterpenoids	FPP	Abscisic acid, C_{15}- lactones	Oils, resins
20	Diterpenoids	GGPP	Gibberellins	Resins
25	Sesterterpenoids	GFPP	-	Resins, bitters
30	Triterpenoids	Squalene	Phytosterols cardenolides, saponins	Resins, bitters, latex
40	Carotenoids	Phytoene		Green tissue, roots, fruit
10^3-10^4	Rubbers	GGPP		Latex, roots

The immense variety of structural types found in the terpenoids, was rationalised by the "Biogenetic Isoprene rule" of Ruzicka in 1953, which was based on the fragmentary knowledge of biosynthesis, available at that time. However, the number of exceptions to the regular arrangement of isoprene units, led to the biogenetic isoprene rule, which encompassed the possibility of rearrangements during biosynthesis. Terpenoids are thus seen as being formed from linear arrangements of isoprene units followed by various cyclisations and re-arrangements of the carbon skeleton. They can also be biosynthetically modified by the loss or addition of carbon atoms. It is useful to classify terpenoids according to the number of isoprene units, from which they are biogenetically derived, even though some carbons may have been added or lost [3-5].

The biogenetic isoprene rule implies the involvement of a branched five-carbon unit, in the biosynthesis of terpenoids. Isoprene, although a natural product, is not a precursor of the terpenoids. The biosynthetic origin of this five-carbon unit is established *via* a common pathway, named the acetate–mevalonate pathway Fig. (**1**). The sequence starts with condensation of three molecules acetyl-CoA forming the important intermediate 3-hydroxy-3-methyl-glutaryl-CoA. The enzyme HMGCoA-reductase catalyses the formation of mevalonic acid (MVA) and is known to be a key enzyme of the acetate–mevalonate pathway. Subsequently, isopentenyl diphosphate (IPP) is biosynthesized by subsequent phosphorylations and

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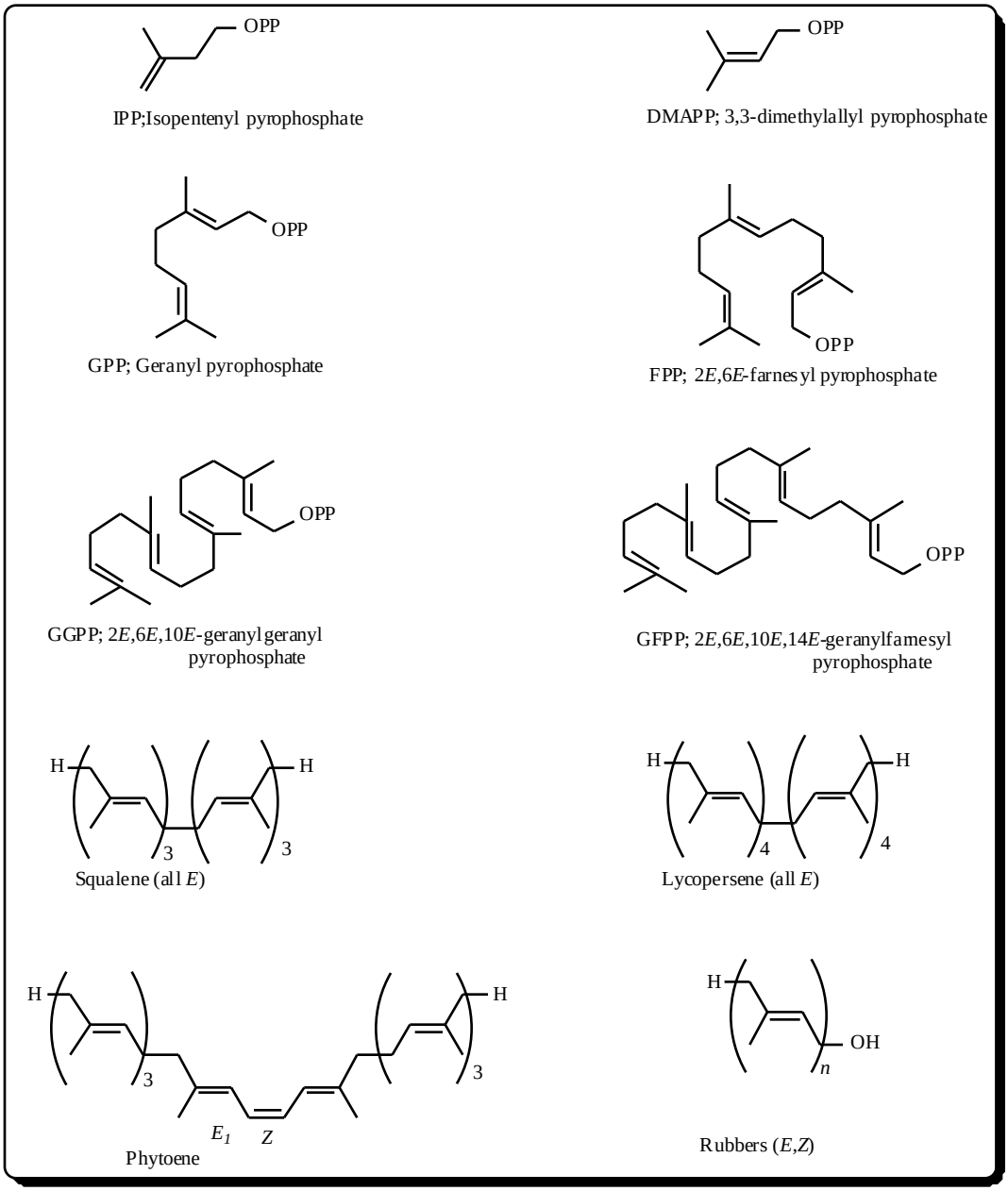


decarboxylation. IPP and its isomer dimethylallyl diphosphate are activated biogenetic precursors of the linear branching point molecules in isoprenoid biosynthesis, geranyl diphosphate (GPP), farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP), respectively. Further investigations by different groups revealed that the concept of a unique biosynthesis of isoprenic units cannot be accepted any longer.

These recent studies have revealed that many bacteria, green algae and chloroplasts of higher plants (as in the leaves of *Stevia rebaudiana* Bertoni) utilise a MVA-independent pathway for the formation of the isoprene skeleton Fig. (**2**). In higher plants a rather clear-cut dichotomy was found: the MVA pathway operates in the cytoplasm, whereas the alternative pathway is located in the plastids. In this alternative pathway the first C_5 intermediate, 1-deoxy-**D**-xylulose-5-phosphate **4** (DXP) is formed from pyruvate **2** and **D**-glyceraldehyde 3-phosphate **3** by a thiamine diphosphate-dependent synthase. A reducto isomerase catalyses the rearrangement of the DXP chain as well as the subsequent NADPH-dependent reduction of the resulting aldehyde to form 2-*C*-methyl-**D**-erythritol 4-phosphate **5** (MEP), which might represent the first committed intermediate in this metabolic pathway. Additional known steps involve the conversion of MEP into ME 2,4-cyclodiphosphate *via* 4-diphosphocytidyl ME and 4-diphosphocytidyl ME 2-phosphate. The remaining steps leading to IPP **6** are unknown and involve reduction and the elimination of water molecules. In the leaves of the plant *Stevia rebaudiana*, in which large amounts of sweet diterpene glycosides (stevioside derivatives) belonging to the *ent*-kaurene series, are produced, their biosynthesis has been studied thoroughly Fig. (**2**). The biosynthesis of the diterpene skeleton, starts, parallel to the gibberelline biosynthesis, with the condensation of dimethylallyl diphosphate (DMAPP) **7** and 3 IPP molecules, resulting in geranylgeranyl pyrophosphate

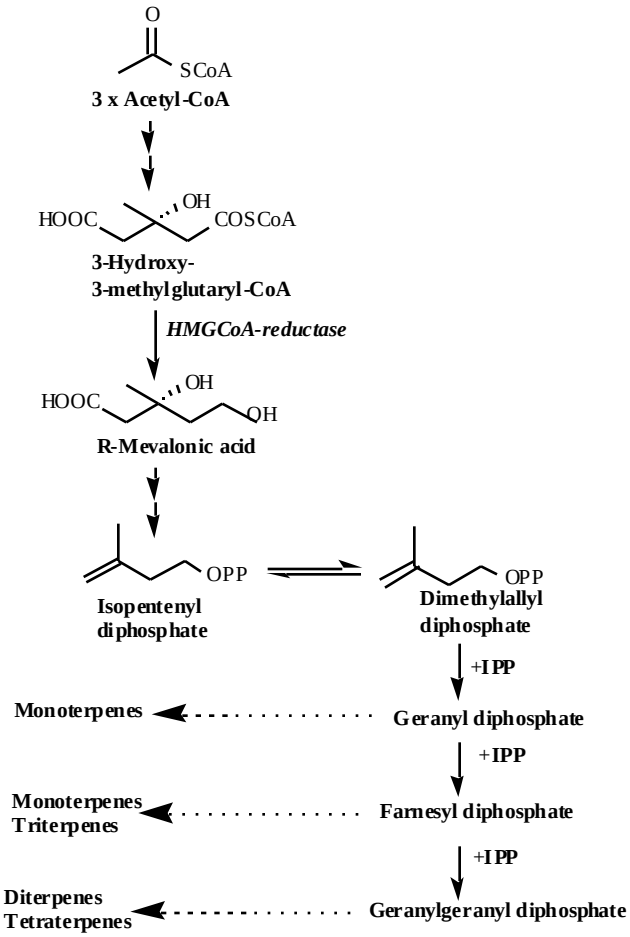


Fig. (1). Isoprenoid biosynthesis *via* the acetate–mevalonate pathway.

(GGPP) **8**. GGPP is cyclised and rearranged to *ent*-kaurene **9**. The conversion of IPP to *ent*-kaurene occurs in the chloroplast. *ent*-Kaurene is oxidised in subsequent steps to *ent*-kaurenoic acid by microsomal mono oxygenases. The branching point with the gibberelline **11** biosynthesis corresponds to the hydroxylation of this *ent*-kaurenoic acid at C-13, affording steviol **10**, the precursor of the sweet diterpene glycosides. Subsequent glycosylation of steviol results in steviolmonoside, steviolbioside, stevioside and rebaudioside [6,7,8,9].

The diterpenoids (C-20) constitute a large group of compounds derived from 2E, 6E, 10 E-geranylgeranyl pyrophosphate. They are found in higher plants, fungi, insects and marine organisms. Of all the families of natural products (many of them have been isolated from Asteraceae and Lamiaceae), the diterpenoids have one of the widest ranges of biological activities. The plant growth hormones gibberellins are included among them, the clerodane bitter principles and insect anti feedants, marine anti-fouling agents, the labdane type sweetener stevioside, tumour inhibitors, co-carcinogens as well as many compounds possessing strong antibiotic activities. Recent interest has centered on the abortifacient isocupressic acid and the anti-hypertensive agent forskolin. Besides, degradation products of sclareol has an interesting role in the perfumery industry. The diterpenoids may be classified in :

A. Acyclic diterpenoids and their derivatives

B. Bicyclic diterpenoids

The clearest classification of the cyclic diterpenoids is based on biogenetic considerations. There are two general modes of cyclisation. The first mode of cyclisation is characteristic of the lower terpenes and is initiated by the terminal pyrophosphate of geranylgeranyl pyrophosphate acting as a leaving group and generating a formal carbocation that alkylates a double bond, often that of the starter isopropylidene unit, which lead to a family of macrocyclic diterpenoids, and their further cyclisation products Fig. (**3**). The major mode of cyclisation is initiated by protonation of the double bond of the starter isopropylidene unit and leads to the formation of bicyclic perhydronaphthalene derivatives. This has its parallel in higher terpenoid biogenesis in the cyclisation of squalene and its epoxide. Subsequent cyclisations are then initiated by the pyrophosphate acting as a leaving group Fig. (**4**). Many of these cyclisation processes

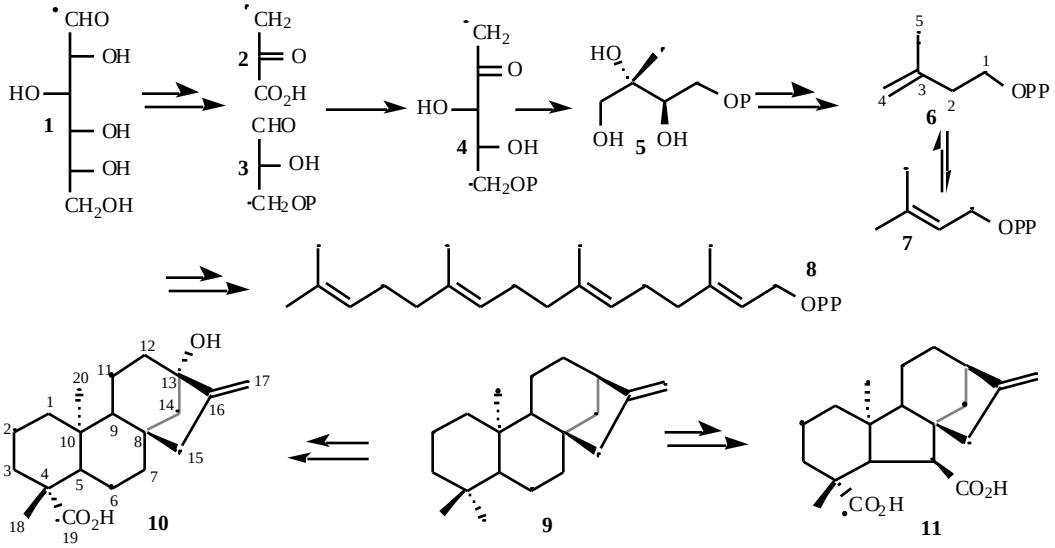


Fig. (2). Steviol biosynthesis from [1-^{13}C]glucose *via* glycolysis and the MEP pathway.

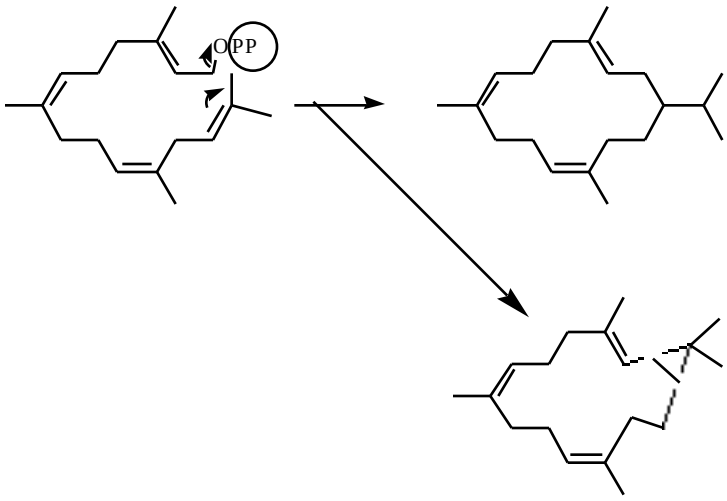


Fig. (3). Macrocyclic diterpenoids and their cyclisation products.

are then further skeletal rearangements as in the formation of the clerodanes and gibberellins [5,10-11].

Labdane Type Diterpenes- Biosynthesis

A large number of diterpenoids, possessing a labdane skeleton, occur in nature Fig. (**5**). They comprise a decalin system and a C-6 ring, which may be open or closed with an oxygen atom, as in manoyl oxide and its derivatives.

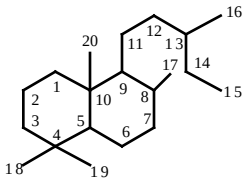


Fig. (5). Basic labdane skeleton.

Labdanes, belonging to the bicyclic diterpenoids group, derived *via* **1** and *ent*-labdanes derived *via* **2**, are of widespread occurrence but few biosynthetic studies have been reported. It has been suggested that they may be derived from GGPP [11] by a two–step process *via* monocyclic intermediates on the basis that both labdane and retinenes co-occur in different populations of *Bellardia trixago* [12, 13]. Another point of biosynthetic interest is the reported co-occurrence of labdanes in both enantiomeric series (normal and antipodal A/B ring junctions- ent-labdanes). This may arise through the occurrence of two different types cyclases, cyclase I ("retro"), which leads from geranylgeranyl diphosphate to (+)-labdadienyl diphosphate, and cyclase II, which leads from geranylgeranyl diphosphate to (-)-labdadienyl diphosphate. For example, the enantiomers **3** and **4** occur in the resin of *Eperua purpurea* [14], the normal labdandiol **6** and antipodal *ent*-labdenol **5** in the leaves of the Brazilian medicinal plant *Mimosa hostilis* and *ent*-sclarene **7** and **8** sclarene have been isolated from different specimens of *Dacridium intermedium* [15]. The co-occurrence of enantiomeric labdanes, is discussed by Carman and Duffield [16].

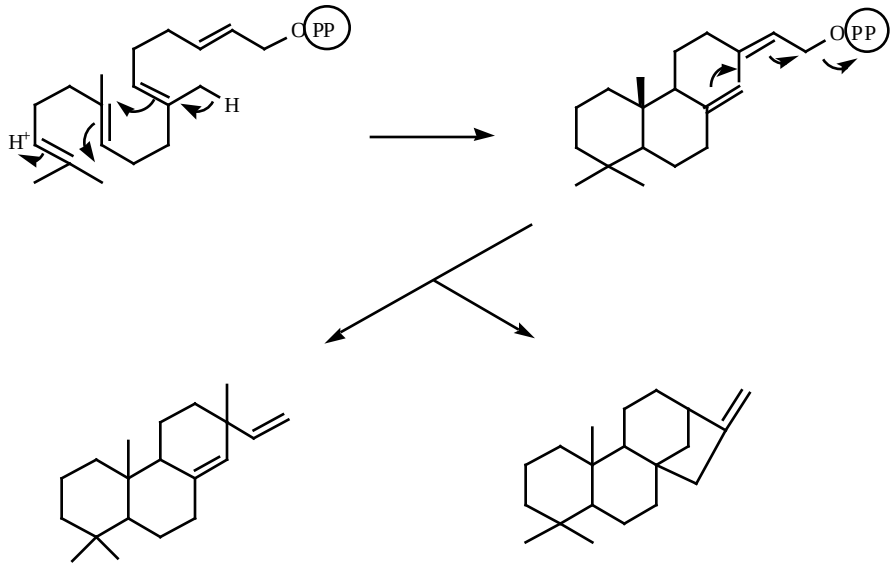
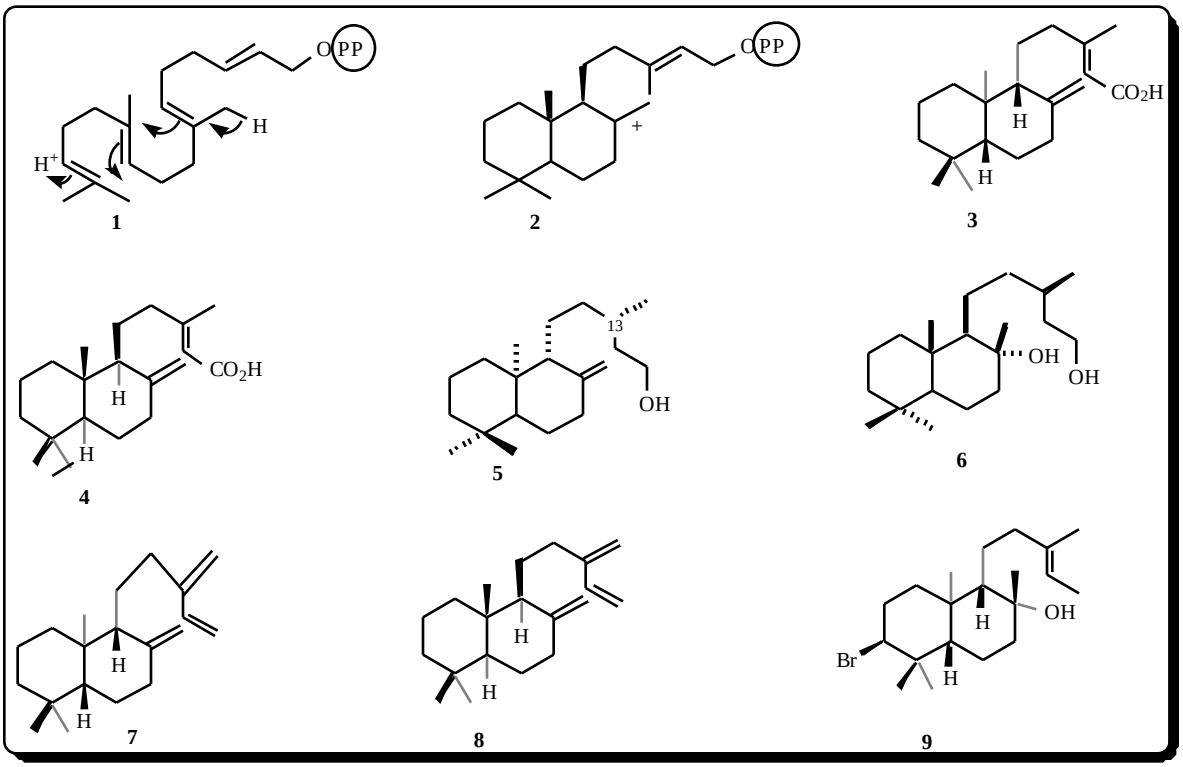


Fig. (4). Cyclisations initiated by the pyrophosphate acting as a leaving group.



The biosynthesis of "normal" labdanes has been investigated in tobacco (*Nicotiana tabaccum* L.)[16]. Labdanediol and sclareol were both formed from GGPP in cell free extracts of a cultivar, 24A, of tobacco. The enzyme activities for the formation of each product were not separated after protein purification, or by thermal inactivation or in product inhibition studies. It was therefore concluded that labdanediol **6** and sclareol **10** are the direct products of one synthase, operating on GGPP. Although these products appear to require hydrolysis of the diphosphate, they could also arise from an aborted Type A cyclisation whereby the allylic carbonium ion is captured by H_2O; thus a diphosphate would not be required.

The occurrence of the 3-bromo-*ent*-labdane, aplysin-20 **9** from the mollusc *Aplysia kurodai* [17], suggests that Type B cyclisation can be initiated by Br+ (bromonium ion) as well as H^+.

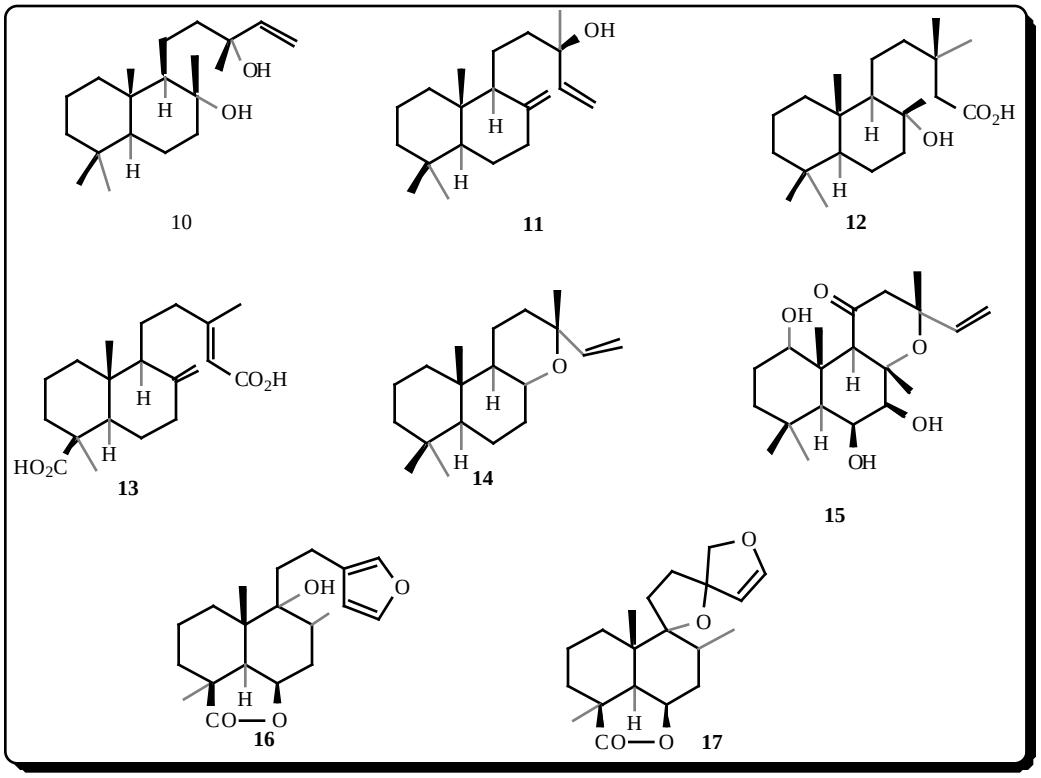


Table 2. Bioactive Labdane-Type Diterpenes from Marine Organisms

Marine Species	Activities	References
Agelas mauritiana	Cytotoxicity, Inhibitors of adenosine transferase	[35, 68]
Dysidea sp	inhibiting the activity of enzyme aldose reductase	[32, 33, 68]
Halichondriidae	Antifungal activity, inhibitors of phospholipase A2	[34, 68, 72]
Lissoclinum voeltzkowi	Cytotoxicity	[43, 44].
Trimusculus conica, Trimusculus reticulatus	Repellent for predatory starfish	[36, 39]
Trimusculus costatus	Toxic to *Artemia salina* and inhibitor feeding of the predatory fish *Pomadasys commersonnii*	[38]
Trimusculus peruvianus	Antimicrobial activity	[37, 38, 40, 107]
Mycale	Cytotoxicity; antiviral, antimicrobial activities	[45, 68]

Further more although the majority of the diterpenoids possess a *trans* relationship between H-9 and the C-10 methyl group, there are some examples of compounds that must be derived *via* a bicyclic precursor with a *cis* relationship between H-9 and the C-10 methyl group [18,19]. Subsequent modifications of the labdanediol may lead to compounds related to manool **11** and to labdanolic acid **12** [20] and agathic acid **13** and its derivatives. In both these series a new chiral centre is created at C-13. Other series of modifications includes the formation of an 8:13-ether as in manoyl oxide **14** or the high oxidised member of this series, forskolin **15** (isolated from *Coleus forskohlii*.) [21]. A modification of the side chain involves the formation of a furan ring as in the diterpenoid bitter principle marrubiin **16** [22]. In some plant species each oxidative stages leading to the furan ring have been isolated. A number of 9:13 prefuran ethers **17** have been found and isolated [23].

ORIGIN OF LABDANES

The labdane type diterpens have been found as secondary metabolites in tissues of fungi, insects, marine organisms, and in essential oils, resins and tissues of higher plants.

Labdane-Type Diterpenes in Fungi, Marine Organisms and Insects

The fungus *Oidiodendron truncate* was isolated from an extreme location, the top Enlang mountain (4.000m) in China, belongs to the division Deuteromycota and is an anamorphic genus of the telomorphic genera Myxotrichum and Byssoascus. From this material several labdane diterpene derivatives have been isolated [24].

A number of labdanes have been obtained from marine organisms Table **2**. From the green algae *Caulerpa trifaria* [25] and *Spongia officinalis* [26], the red algae *Laurencia sp., L. pinnata, L. venusta* [27-29] and *Chondria tenuissima* [30] and brown alga *Taonia atomaria* [31]. From the marine sponges *Dysidea sp.,* (dark brown sponge)[32,33], *Halichondriidae***,** [34](orange sponge), *Agelas mauritiana* [35], the marine pulmonate gastropod *Trimusculus conical, T. costatus, T. reticulatus* and *T. peruvianus,* [36-40] as well as in *Aplysia dactylomela* [41]. Some labdane glycerides have been also isolated from the antarctic nudibranch *Austrodoris kerguelensis* [42] from the marine tunicate *Lissoclinum voeltzkowi* (Urochordata)[43,44], from the frozen Thai sponge belonging to the genus *Mycale* [45] as well as from the Mediterranean sponge *Raspaciona aculeata* [46].

Several labdne diterpenes have been isolated from the wax exuded by the scale insect *Ceroplastes pseudoceriferus* (Coccidae) Hemiptera Table **3**. It is noteworthy, that the configurations of the labdanediene alcohols were antipodal to the ordinary labdanes isolated from terrestrial plants [47]. Besides, a known source of labdane-type diterpenes is propolis. Propolis is a resinous hive product, produced from honeybees (*Apis mellifera*), from various plant sources, extensively used in food, beverage and in folk medicine [48,49].

Table 3. Labdane-Type Diterpenes from Insects

Insects	References
Ceroplastes pseudoceriferus (Coccidae) Hemiptera	[47]

Labdane-Type Diterpenes in Plants

Labdane-type diterpenes have been isolated from several plant families such as: Acanthaceae, Alismaceae, Annonaceae, Apocynaceae, Aristolochiaceae, Asteraceae, Caprifoliaceae, Cistaceae, Cupressaceae, Cyperaceae, Euphorbiaceae, Labiatae, Leguminosae, Lythraceae, Meliaceae, Nolanaceae, Pinaceae, Podocarpaceae, Polemoniaceae, Potamogetonaceae, Rosaceae, Rhizophoraceae, *Sapindaceae*, Scrophulariaceae, Solanaceae, Taxodiaceae, Velloziaceae, Verbenaceae, and Zingiberaceae (Table **4**).

Among them, the gymnosperms as well as families Asteraceae, Lamiaceae and Zingiberaceae are the most important sources of labdane diterpenoids. As labdanes are distributed among all conifers, they could be used as chemosystematics markers [50]. Besides, through studies on the terpenoid compositions of conifer trees from the Miocene Clarkia flora (Cupressaceae s.l.), Emerald Creek, Idaho,

Table 4. Bioactive Labdane-Type Diterpenes from Plant Families-Fungi

Species	Activities	References
Acanthaceae		
Andrographis paniculata	Against *E. coli* enterotoxin in *in vivo* models, anti-PAF activity, against common cold, anti-malarial activity, hepatoprotective activity, analgesic, anti-pyretic and anti-ulcerogenic effects, cytotoxicity.	[85, 114, 146, 178-182, 188-191, 239]
Andrographis wightiana	Medicinal herb found in the Annamalais Hills of India	[246]
Alismaceae		
Echinodorus macrophyllus	Brazilian medicinal plant ("Chapeu-decouro"),	[247]
Annonaceae		
Neouvaria acuminatissima	Cytotoxicity	[68, 111, 149]
Polyalthia macropoda	Against *Leishmania donovani*	[149]
Apocynaceae		
Melodinus monogynus	Cardiotonic activity	[230]
Aristolochiaceae		
Asteraceae		
Agathis lanceolata	Inhibitor of Superoxide Anion Radical Release	[162]
Alomia myriadenia	Cytotoxic activity, activity against *Trypanosoma cruzi*	[142-144, 248]
Aster oharai	Cytotoxic activity	[120]
Baccharis gaudichaudiana, Baccharis scoparia, Baccharis sternbergiana, Baccharis species:*, B. concave, B. petiolata a, B. confertifolia, B. paniculata,* B. pingraea	Natural sweetening agents cytotoxicity	[128, 168].
Chrysoma (ex. *Solidago*) *pauciflosculosa*	Reduce the germination of various grasses	[249].
Grindelia acutifolia ,G . camporum, G. discoidea, G. havardii	Aphid-deterrent activity	[203]
G. humilis, G. paludosa, G. stricta	Aphid-deterrent activity	[202-207]
Haplopappus chrysanthemifolius	Antimicrobial activity	[100, 101]
Helichrysum rupestre	Antimicrobial activity	[99]
Isocoma coronopifolia, I. tenuisecta	Natural insecticides	[208]
Metasequoia glyptostroboides	Antifungal activity	[83, 84]
Phlogacanthus thyrsiflorus	Bronchial Conditions the Indian Medicinal plant	[228]
Stevia rebaudiana	Sweetening agent, antihyperglycaemic activity, hypotension and marked decrease in heart rate	[172, 201, 241-245]
Xanthocephalum gymnospermoides var *eradiatum*	Phytotoxic activities	[218, 219]
Caprifoliaceae		
Viburnum suspensum	Antibacterial activity	[76, 77]
Cistaceae		
Cistus creticus	Cytotoxic activity against human leukemic cell lines, strong antimicrobial activities against human pathogenic bacteria and fungi	[86, 88, 89, 91, 96, 97, 124-126]
Cistus creticus subsp. eriocephalus	Antimicrobial, cytotoxic activities	[89-93]
Cistus incanus ssp. i*ncanus*	Antimicrobial, strong cytotoxic activities	94, [95, 122, 127]
Cistus monspeliensis	Antimicrobial, cytotoxic, antioxidant activities	[94, 95, 123, 163]
Cupressaceae		

(Table 4). contd.....

Species	Activities	References
Calocedrus formosana	Abortifacient activity in cattles and sheeps	[174]
Chamaecyparis obtusa	Antifeedant activity	[213, 214]
Cupressus macrocarpa, Cupressus sempervirens	Abortifacient activity in cattles and sheeps	[173-176, 250]
Cryptomeria japonica	Abortifacient	[173-175]
Juniperus communis (Shug Chher)	Platelet aggregation inhibitor	[199]
Juniperus chinensis	Abortifacient activity in cattles and sheeps	[173-175]
Juniperus excelsa	Antimycobacterial, cytotoxic activities	[105]
J. procera	Antimycobacterial activity, potential antitermite natural pesticide	[68, 81, 213, 214]
*Platycladus orientalis (*ex. *Biota orientalis)*	Anti-PAF activity, antimalarial	[148, 195-198]
Thuja standishii (Gord) Carr.	cytotoxicity	[137, 138]
Cyperaceae		
Euphorbiaceae		
Cluytia abyssinica, C. richardiana	Hypoglycemic effect	[170, 171]
Excoecaria agallocha	Anti-tumour-promoters, induction of Epstein-Barr virus early antigen (EBV-EA)	[117, 118]
Croton oblongifolius Roxb.	Cytotoxicity	[139, 140]
Lamiaceae		
Coleus forskohlii	Anti-hypertensive activity	[18, 69, 129,-135, 157-159, 177, 200]
Hyptis spicigera	Anti-insect activity	[116, 209]
Lagochilus hirsutissimus	Hemostatic activity	[229]
Leonotis nepetaefolia	Treating skin infections	[235]
Leonurus heterophyllus	Immune system	[69, 192-192]
Moldenhavera nutans	Antivirus activity	[145]
Phlomis medicinalis, P. younghushband	Against cough and fever	[236]
Plectranthus fruticosus L´Herit.	Antimicrobial activity	[103, 104]
Salvia candidissima		[105]
Salvia linariaefolia	strong antibacterial activity	[74]
Salvia palestina	antimicrobial activity	[73]
Sideritis hirsuta, S. nutans, S. perfoliata	Against *Leishmania donovani*	[150-154]
Sideritis javalabrensis	Anti-inflammatory activity	[160, 161, 183, 184]
S. varoi subsp. cuatrecasasii, subsp. nijarensis	Inhibitors of the growth of the promastigote and amastigote forms of *Leishmania donovani*	[150-152]
Stachys chrysantha	Antibacterial activity	[98]
Leguminosae		
Copaifera L. species	Antimicrobial activity, cosmetic purposes	[82, 222-224]
Lythraceae		
Meliaceae		
Mimosaceae		
Nolanaceae		
Pinaceae		

(Table 4). contd.....

Species	Activities	References
Picea glehni	Potent inhibitory effects on Epstein-Barr virus early antigen (EBV-EA)	[121]
Pinus armandii, P.contorta, P. jeffreyi	Abortifacient activity in cattles and sheeps	[175]
Pinus ponderosa, Pinus sibirica	Abortifacient activity in cattles and sheeps	[173-176, 251]
Podocarpaceae		
Polemoniaceae		
Potamogetonaceae		
Potamogeton natans	Anti-algal, phytotoxic activities	[215-217]
Potamogeton nodosus	Antibacterial activity	[80, 81]
Potamogeton malaianus	Antimycobacterial activity, antiviral, cytotoxicity	[106]
Ruppia maritima	Anti-algal, phytotoxic activities	[215, 216]
Rosaceae		
Rubus suavissimus (*Rubus chingii)*	Sweetening agent	[169]
Rhizophoraceae		
Sapindaceae		
Dodonaea viscosa	Plant used in Traditional Medicine, antimicrobial, spasmolytic activity on the isolated rat ileum, smooth muscle relaxing activity	[231-234]
Scrophulariaceae		
Scoparia dulcis	Paraguayan drug *Typycha Kuratu,* β-glucuronidase inhibitor	[164, 166]
Solanaceae		
Taxodiaceae		
Cryptomeria japonica	Against wound eczemas, anti-inflammatory activity	[185]
Velloziaceae		
Verbenaceae		
Premna oligotricha	Antibacterial activity	[75]
Vitex rotundifolia	Medicinal plant known as “Mankeishi, anti-mutagenic activity, against headaches, potential chemopreventive and chemotherapeutic agent	[109, 110, 252]
Zingiberaceae		
Aframomum aulacocarpos	Antimicrobial, cytotoxic activity	[253]
Aframomum danielli	West African food spice condiment, antileukemic activity	[221]
Aframomum latifolium, A. sceptrum	Antiplasmodial activity	[147]
Alpinia calcarata	Cytotoxic activity	[119]
Alpinia paniculata, A. sceptrum	Antimalarial activity	[147]
Alpinia galanga.	Flavouring purposes	[220]
Alpinia zerumbet	Chinese medicine for stomach problems	[254]
Hedychium coronarium	Cytotoxic, anti-inflammatory activities	[114, 115, 185-187]
Renealmia alpinia	Cytotoxic activity	[112, 113]
Zingiber mioga Roscoe	Cytotoxicity	[141]
Liverworts		
Propolis	Antibacterial, cytotoxic, hepatoprotective activities	[48, 49, 78, 136]
Fungi		
Oidiodendron truncata	Antimicrobial, herbicidal activities\1	[24]

USA, and of related extant species (*Taxodium dubium*, *Glyptostrobus oregonensis*, and *Cunninghamia chaneyi* etc.), it has been shown that terpenoids among which labdanes are valuable molecular markers for (paleo)-systematics and phylogeny of conifers [51].

Several labdanes have also been also isolated from liverworts' genera (Frullania [52], Gleichenia[53], Jamesoniella autumnalis [54-56], Jungermannia infusca[57], J. vulcanicola [58-60], Nardia scalaris, N. succulents [61], Pallavicinia subciliata [62,63], Pleurozia acinosa [64], Ptychanthus striatus [65,66], and Scapania undulate [67].

BIOLOGICAL ACTIVITIES

The diterpenes of labdane type have been reported to have broad spectrum of biological activities [68-72].

Antimicrobial Activities

From the fugus *Oidiodendron truncata*, [24] several labdane diterpene derivatives (Fig. (**6**) oidiolactones) were isolated, which exerted antifungal activities against *Ustilago violacea, Eurotium repens, Mycophyta microspora* as well as moderate antibacterial activities against *E. coli* and *Bacillus megaterium*.

Labdanes from the Thai sponge *Mycale*, exhibited, antibacterial activities by inhibiting the growth of Gram-positive bacteria *B. subtilis* and *S. aureus* [45, 68]. While diterpenoids of the same class were isolated from the dark brown sponge *Halichondriidae* and inhibited the growth of *S. aureus* at a concentration of 5µg/disk and *B. subtilis* at 50µg/disk in *in vitro* antimicrobial assays and also inhibited the growth of *C. albicans* at a concentration of 5µg/disk [34, 72]. The marine gastropod mollusk *Trimusculus peruvianus*, collected on the coast of central Chile yielded new labdane metabolites, which showed moderate antimicrobial activities [40].

The labdane type diterpene, sclareol from the plant *Salvia palestina*, is well known to possess strong antimicrobial activity [73], while new labdane diterpenes, from *Salvia linariefolia* (Lamiaceae), and *Premna oligotricha* (Verbenaceae) are also reported to possess strong antibacterial activities [74, 75] against *Staphylococcus aureus*. Especially, studies on *Premna oligotricha* afforded *ent*-12-oxolabda-8,13-dien-15-oic acid and several other labdane type diterpenes. The above referred plant is a shrub occurring widely in East Africa. Its twigs are used as chewing sticks while the smoke formed by burning the plant is used to sterilise the milk containers. Its crude ethanolic extract showed antibacterial activity against a wide range of Gram + bacteria [75].

Labdane glycosides have been described as constituents of *Viburnum suspensum* (Caprifoliacae). These labdanes (gomojosides A-J) were found to exhibit antibacterial activity against *E.coli* [76, 77]. From the bark of *Juniperus procera* were isolated two known labdane diterpenes, cryptotrienolic acid and isocupressic acid. These diterpenes were tested against several bacteria and the first appeared a weak activity while the latter appeared inactive at all [68].

Several labdane type diterpenes have been isolated from Brazilian propolis [48, 49, 78] with strong antibacterial activity and special activity against *Helicobacter pylori*. From *Potamogeton nodosus* (Potamogetonaceae) furanoid labdane-type diterpene were found to exhibit moderate activity against a number of both Gram-positive and Gram-negative bacteria, while the ethanol extract of the plant revealed as antibacterial activity [79, 80]. The bark of *Juniperus procera* (Cupressaceae) yielded several labdane-type diterpenes with strong activities against *Mycobacterium* species [81]. Several antimicrobial labdanes from the oleoresin of the Peruvian Medicinal plant *Copaifera paupera* (Leguminosae) have also been studied and published recently. Several compounds among them coppalic acid and kaurenoic acids, showed significant antimicrobial activity (MIC 10µg/ml) against Gram-positive bacteria, comparable with cephotaxime used as control [82].

The antifungal activity of the labdane diterpenes (metasequoic acids A and B) of *Metasequoia glyptostroboides* (Asteraceae) has also been noted [83, 84].

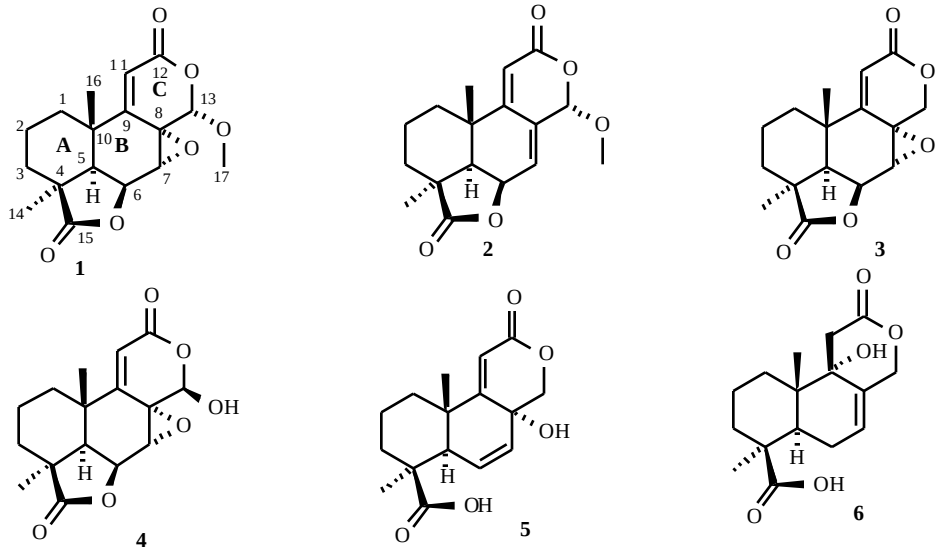


Fig. (6). Structure of oidiolactones (**1**-**6**)

Strong anti-diarrhoeal activity of diterpenes of *Andrographis paniculata* (Acanthaceae) against *E. coli* enterotoxin in *in vivo* models has been showed [85]. Also antibacterial activity from labdane diterpenes from dried leaves o *Cistus incanus* sp. *creticus* has been assayed, against Gram(+) bacteria *S. aureus* and *S. epidermidis*, Gram (-) *P. aeruginosae, E. cloaceae*, *K. pneumoniae* and *E. coli*, as well as for their antifungal activity against *C. albicans*, *C. glabrata* and *S. cerevisiae*. The majority of the assayed compounds showed significant activities against *S. aureus*, *P. aeruginosa* and *K. pneumoniae* [86-88]. The constituents and the essential oil extracted either from the leaves or from the resin of the same plant, as well as from *C. creticus* sp. *eriocephalus* which was found to have as major constituents manoyl derivatives exhibited also strong antiumicrobial activities when it was tested against Gram (+) bacteria and against the human pathogenic fungi *C. albicans* [88-93]. The essential oils also from *Cistus parviflorus* and *Cistus monspeliensis* have been tested against several bacterial strains showing only the oil of *Cistus monspeliensis* strong activity, in which labdane diterpens were found as major compounds. The methanolic extract of *C. incanus* and *C. monspeliensis* showed strong inhibitory activity *in vitro* against five strains of bacteria and five strains of fungi [94, 95]. Twenty-five semisynthetic labdane-type diterpenes derived from the two major natural compounds of the resin "ladano" of *Cistus creticus*, five among all the chloroethyl carbamidic esters showed the strongest antimicrobial activities against Gram positive and negative bacteria as well as against three human pathogenic fungi [96, 97].

The essential oils of the aerial plants of the Greek plant *Stachys chrysantha* (Lamiaceae) and of *Helichrysum rupestre* (Asteraceae) growing in the Balearic Islands, exhibited also strong antimicrobial activity against six Gram positive and negative bacteria probably associated with their high manoyl oxide content [98, 99]. *Haplopappus chrysanthemifolius* (Asteraceae) is another source of labdabe diterpenoids, exhibiting a special activity against *B. cereus* [100,101]. Labdane type diterpenes (epigomeric and gomeric acids) from several Spanish Lamiaceae species (*Sideritis* sp.) have been assayed for their antibacterial activities against Gram positive and Gram negative bacteria, exhibiting remarkable activity especially against Gram positive ones [102].

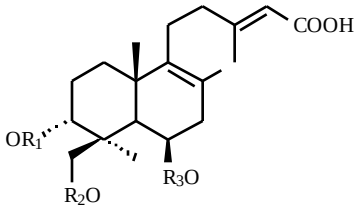
Several labdane diterpenoids have been isolated from *Plectranthus fruticosus* L'Herit. (Lamiaceae) were tested as antimicrobial agents against three bacteria strains and one yeast strain, showing moderate inhibitory activity mostly against *Staphylococcus aureus* [103,104].

Antituberculosis Activity

A new labdane type diterpene, isolated from the berries of *Juniperus excelsa*, (uniperexcelsic acid) and a furanoid labdane-type diterpene from *Potamogeton malaianus* were found to be moderately active against *Mycobacterium tuberculosis* [105, 106].

Cytotoxic Activities

Mycaperoxides A and B isolated from the sponge *Mycale sp*. showed significant cytotoxicity (IC50= 0.5-1.0μg/ml) against cell lines of P-388, A-549 and HT-29 [41, 68]. Examination of the marine tunicate *Lissoclinum voeltzkowi* (Urochordata) gave highly cytotoxic rare succinimide, dichlorolissoclimides [43, 44], while two labdanes (agelasimine A and B) isolated from the marine orange sponge *Agelas mauritiana*, were exhibited strong cytotoxicity, when tested against L-1210 mouse leukaemia cells *in vitro* (ED50=2-4μg/ml) [35, 68]. Four new labdane diterpenes, **1-4** with an unusual oxidation pattern have been isolated from the marine pulmonate *Trimusculus peruvianus* Fig. (**7**). These compounds exhibit *in vitro* moderate cytotoxic activity against human colon carcinoma cell lines [107].



1. $R_1=R_2=R_3=H$
2. $R_1=COC_4H_9$, $R_2=R_3=H$
3. $R_1=R_3=COC_4H_9$, $R_2=H$
4. $R_1=R_2=COC_4H_9$, $R_3=H$

Fig. (7). Labdane diterpenes, **1-4** from *Trimusculus peruvianus*.

Related compounds to **1-4** have been found in terrestrial plants, such as *Amphiachyris amoena* (Shinners) Solbrig (Asteraceae) exhibiting comparable cytotoxity [108].

Anti-mutagenic activity has been associated with the presence of polylacthic acid in the extracts of the Asian medicinal plant known as "Mankeishi" obtained from *Vitex rotundifloria* [109]. The inhibitory effect of rotundifuran, a labdane type diterpene from the fruit of *Vitex rotundifolia*, on the proliferation of human myeloid leukaemia HL-60 cells was examined. The compound showed that induces apoptosis, in the above referred cells, which was judged by the morphological alteration of the cells and by the detection of DNA fragmentation using agarose gel electrophoresis. The degree of apoptosis was quantified by a sandwich enzyme immunoassay and flowcytometric analysis. The final suggests that the isolated compound may be used as a potential chemopreventive and chemotherapeutic agent [110].

The interesting cytotoxic lactone, accuminolide from *Neouvaria acuminatissima* (Annonaceae) showed significant activity against a number of human cancer cell lines [68, 111].

From the berries of *Juniperus excelsa* a new labdane type diterpene was isolated and elucidated as 3α-acetoxylabda-8(17),13(16),14-trien-19-oic acid (juniperexcelsic acid). Cytotoxic activity of the hexane extracts was investigated against a panel of cell line and found highly active against LnaP, KB-V(+VLB) and KB-V(-VLB) cell lines [105].

Cytotoxic activity from the labdans from *Renealmia alpinia* (Zingiberaceae) testing them in the yeast Sc-7 assay gave a positive response, indicative of cytotoxic activity [112,113]. From the plants *Andrographis paniculata* (Acanthaceae) and *Hedychium coronarium* (Zingiberaceae) several cytotoxic compounds have been isolated and assayed [114,115]. From the medicinal Mexican plant *Hyptis*

spicigera (Lamiaceae) a new natural compound (spicigerolide) was isolated possessing strong cytotoxic activity on KB cell line [116]. Several diterpenoids have been isolated from the resinous wood of *Excoecaria agallocha* (Euphorbiaceae) and their inhibitory effects on the induction of Epstein-Barr virus early antigen (EBV-EA) in Raji cells were examined to search for potent anti-tumour-promoters from natural resources. Of these compounds, secolabdane type diterpenes exhibited a remarkable inhibitory effect on EBV-EA induction, and a significant anti-tumour promoting effect *in vivo* on a two-stage carcinogenesis test of mouse tumour using 7,12-dimethylbenz[a]anthracene (DMBA) as initiator and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) as promoter [117,118].

Two novel bis-labdanic diterpenoids (calcaratarin D and E) from *Alpinia calcarata* (Zingiberaceae) were showed cytotoxic activity against human KB cells *in vitro* [119]. The furanoid labdane type diterpenes from *Potamogeton malaianus* were showed to possess cytotoxicity against the Vero cell-line [106]. Thirteen labdanes were isolated from the aerial parts of *Aster oharai* (Asteraceae), which have been used to treat asthma and diuresis in Korean traditional medicine. The isolated labdane diterpenes exhibited cytotoxicity against human colorectal cancer cells 9HCT15), human central nervous system cancer cells (SNB-19) and human skin cancer cells (SK-MEL-2 and LOXIMVI) [120]. Several labdane compounds from *Picea glehni* (Pinaceae) showed potent inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) activation induced by the tumour promoter 12-O-tetradecanoylphorbol 13-acetate. [121].

The extract from leaves of *Cistus incanus* ssp. *incanus* dose-dependently inhibits the enzymatic activities of both alanyl aminopeptidase (APN, CD13, EC 3.4.11.2) and dipeptidylpeptidase IV (DP IV, CD 26, EC 3.4.14.5.) This inhibition is not reversible and very likely results from covalent binding of reactive compounds to the enzymes. Further more, the extracts decrease the DNA- synthesis of human T cells and mononuclear cells and inhibit the proliferation rate of the human T cell line KARPAS-299 in a dose-dependent manner. Data are presented suggesting that the anti-proliferative effects of the extracts are due to their strong cytotoxic activity [122].

Seven diterpenes isolated from *C. incanus* sp. *creticus*, as it has been already referred, were tested *in vitro* against three cancer cell lines (P388 murine leukaemia, KB and non-small cell lung cancer (NSCLC-N6). The assayed labdanes exhibited strong cytotoxic activity while the mixture of sclareol isomers isolated, exhibited IC50 at least as good as 6-mercaptopurin, which was used as control drug [88, 89]. *ent*-13-*epi*-Manoyl oxide and its isomers from *C. monspeliensis* were tested against nine leukaemic cell lines. The results showed that the manoyl oxide isomers as well as ent-13-epi-manoyl oxide exhibited slight growth inhibiting activity [123]. Nine known labdane type diterpenes from *Cistus creticus ssp. creticus* and from the resin "Ladano" which is excreted on the surfaces of the leaves and the stems of the plant, were examined *in vitro* for their cytotoxic activity against 14 human leukaemic cell lines, 13E-labd-13-ene-8alpha,15-diol exhibited cytotoxic activity against 13 of the cell lines tested, while 13E-labd-7,13-dienol was active only against HL60 cells. The first compound was examined for its effect on the uptake of [3H]-thymidine as a marker of DNA synthesis [123,124]. Sclareol was tested for cytotoxic effect against a panel of established human leukaemic cell lines. The compound showed an IC_{50} lower than 20 μg/ml in most cell lines tested while it was higher for testing peripheral blood mononuclear leukocytes (PBML). Further more the compound was tested for cytostatic activity against four leukaemic cell lines. At a concentration of 20μg/ml the compound showed a significant cytostatic effect as soon as 4 hours after continuous incubation against two from B and two from T lineage cell lines. The morphology and the kind of death induced from sclareol in three cell lines has also been investigated. The effect of sclareol on the cell line progression of two cell lines, using flow cytometry was examined. The results show that the compound kills cell lines through the process of apoptosis. The appearance of the apoptotic signs is time and dose dependent. This is the first time that a labdane type diterpene kills tumour cells *via* a phase specific mechanism, which induces apoptosis [124, 125]. Besides sclareol and the thiomidazolide derivative *ent*-3-beta hydroxyl-13-epi-manoyl oxide coming from the fruits of *Cistus creticus* sp. *creticus* were found to induce apoptotic cell death in human T cell leukaemia lines and to interfere with their cell cycle, arresting cells at $G_0/1$ phase. Apoptosis can involve the activation and/or suppression of critical genes, such as c-*myc* whose reduction or its inappropriate expression can be associated with induction of cell death and *bcl*-2 whose activation prevents apoptosis in latter case. In order to detect any concomitant effect of the two compounds upon c-*myc* and *bcl*-2 oncogene expression, a Western blot analysis was performed to determine the levels of expression of these two genes upon treatment with the above compounds. The analysis showed that of c-*myc* proto-oncogene levels were markedly reduced before massive apoptosis ensued in H33AJ-JA1 and MOLT3 cells, while *bcl*-2 expression remained unaffected. The induction of the apoptosis of the tested compounds in these T-cell leukaemic cell lines is preceded by c-myc down regulation and furthermore sustained *bcl*-2 expression does not rescue cells from apoptosis under conditions used [125, 126]. Three labdane type diterpenes, isolated from the hexane extract of leaves from *Cistus creticus* subsp. *eriocephalus (*Viv.) Greuter & Burdet and *Cistus monspeliensis* L. were examined for their *in vitro* cytostatic and cytotoxic activity against nine human leukaemic cell lines, three of which exhibited a multidrug resistant phenotype. The cytostatic and cytotoxic activity of the tested diterpenes followed the order 1 >2 >3. (labd-13(E)-ene,-8 alpha ,15-diol (**1**), labd-13(E)-ene,-8 alpha ,15-yl acetate (**2**) and (+)-19-acetoxy-*cis*-clerodan-3-en-15-oic acid (**3**)) [127]. Epigomeric and gomeric acids have been also tested against HeLa cells and have been found to exhibit IC_{50} at 10μg/ml [102].

Labdane type diterpenes from the series of gauchaudol from(Asteraceae) *Baccharis gaudichaudiana* were found to possess significant cytotoxic activity against P388 and KB-VI (KB cell line resistant to vinblastine) but not against the parental KB cell line (which does not express multi drug resistance MDR) [128].

Finally, several studies concerning the cytotoxic as well as cancer-related properties of forskolin from *Coleus forskholii* have been performed. Forskolin has been suggested that it could be suitable for antitumour

combination chemotherapy as it showed a very strong combined effect when it has been administered with mitomycin C or/and *cis*-diamminedichloroplatinum (DDP) [129, 130]. Dideoxforskolin, a forskolin derivative, inhibits cell death induced by *Pseudomonas*, ricin, modeccin, and diphtheria toxin in MDCK cells [131]. It has also been reported that forskolin decreases proliferation and induces apoptosis in several kind of cancer cells [131,132]. In other studies forskolin was found to reduce the expression of several oncogenes such as c-*myc* mRNA in human skin fibroblasts cell lines, as well as in monocytic cell lines [133-135].

Several labdanes isolated from Brazilian propolis have been tested for their cytotoxic activity towards human HT-1080 fibrosarcoma and murine colon 26-L5 carcinoma cells and showed potent cytotoxicity. It is noteworthy that investigation suggested that *Baccharis* spp., in addition to *Clusia* and *Aurocaria* species are the most significant sources of tropical Brazilian propolis. The referred species are also well-known of labdane-diterpenoids [136].

Seven labdane type diterpenoids from the stem bark of *Thuja standishii* (Gord.) Carr. (Cupressaceae) Fig. (**8**) and their analogues showed strong inhibitory effects on Epstein–Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Among these compounds, 15,16-*bisnor*-13-oxolabda-8(17),11*E*-dien-19-oic acid was revealed to have the strongest inhibitory effect on the EBV-EA activation, being stronger than that of β-carotene which has been intensively studied in cancer prevention using animal models. 15,16-*bisnor*-13-Oxolabda-8(17),11*E*-dien-19-oic acid was also found to exhibit the excellent anti-tumour promoting activity in two-stage mouse skin carcinogenesis test using 7,12-dimethylbenz[*a*]-anthracene and TPA [137, 138].

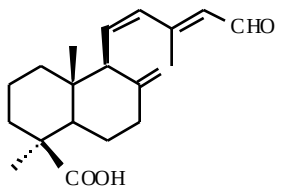


Fig. (8). 15-Oxolabda-8(17),11*Z*,13*E*-trien-19-oic acid from *Thuja standishii*.

Croton oblongifolius Roxb. (Euphorbiaceae) has been used as a traditional medicine for many applications such as for dysmenorrhea, as a purgative, and to treat dyspepsia and dysenteria. Moreover, this plant has been used in conjunction with *C. sublyratus* to treat gastric ulcers and gastric cancers. Labdane type diterpenes from the stem bark of the plant (**1-4)** were tested for their cytotoxicity against human tumour cell lines (Fig. **9**) and compound **3** showed non-specific moderate cytotoxicities against human gastric carcinoma (KATO-3), colon adenocarcinoma (SW 620), breast ductal carcinoma (BT474), liver hepatoblastoma (HEP-G2) and undifferentiated lung carcinoma (CHAGO). Compound **4** was inactive against all cell lines while compound **1** showed weak activity against gastric and colon adenocarcinoma and compound **2** showed weak activity against gastric and breast ductal carcinoma [139, 140].

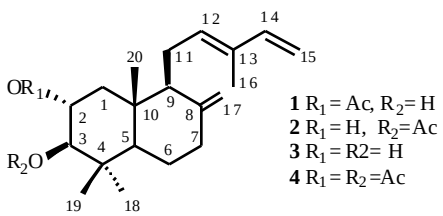


Fig. (9). Labdane type diterpenes from the stem bark.

The effects of the constituents isolated from ginger species including curcumin, 6-gingerol and labdane type diterpene compounds on cell proliferation and the induction of apoptosis in the cultured human T lymphoma Jurkat cells have been studied. Among the tested compounds, Galanals A and B, isolated from the flower buds of a Japanese ginger, myoga (*Zingiber mioga* Roscoe), showed the most potent cytotoxic effect. Exposure of Jurkat human T-cell leukaemia cells to galanals resulted in the induction of apoptotic cell death characterised by DNA fragmentation and caspase-3 activation. The mitochondrial damage pathway was suggested to be involved in galanal-induced apoptosis because the treatment of cells with galanals induced mitochondrial transmembrane potential alteration and cytochrome *c* release. The anti-apoptotic Bcl-2 protein was downregulated by the galanal treatment together with enhancement of the Bax expression. The results from this study provide biological evidence that ginger-specific constituents other than curcuminoids are potential anticancer agents [141].

Myriadenolide (Fig. **10**) is a diterpene recently isolated from the extract of *Alomia myriadenia* Schultz-Bip. ex. Baker (Asteraceae),. It has been shown that this compound induces depolarisation of mitochondrial membranes and apoptosis associated with activation of caspases-8, -9, and -3 in Jurkat and THP-1 cells. Taken together, our results indicate myriadenolide as a novel candidate for the treatment of haematological malignancies [142]. Through a screening program in Brazilian flora, carried out to detect the presence of immunosuppressive compounds by using the *in vitro* phytohaemagglutinin A (PHA)-induced human peripheral blood mononuclear cell (PBMC) proliferation assay, myriadenolide after incubation with human PBMC, showed that it has been reduced significantly the percentage of $CD14^+$ cells, but it has no effect on the relative amount of $CD3^+CD4\text{-}CD8^+$ and $CD3^+CD4^+CD8\text{-}$ T lymphocyte subpopulations. Neither viability nor proliferative competence of T lymphocytes was significantly affected by myriadenolide. The results showed that myriadenolide induces a dose-dependent apoptosis in monocytes and thus

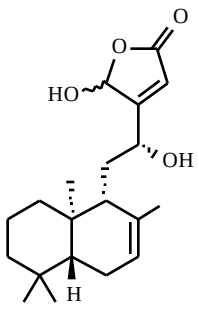


Fig. (10). Chemical structure of myriadenolide.

explain the immunosuppressive effect observed. We reported herein the investigation of a specific target cell within myriadenolide-treated PBMC and diterpene apoptosis induction in monocytes [143, 144].

Antiviral Activity

Labdanes from the Thai sponge *Mycale*, exhibited, antiviral activity (IC_{50} 0.25-1.0μg/ml) against vesicular stomatitis and herpes simplex type-1 virus [45, 68]. Labdane diterpenes (among which a new bis-diterpene, moldenin), isolated from the stems of *Moldenhawera nutans*(Leguminosae) showed weak antivirus activities through HIV-1 RT assay [145]. New furanoid labdane diterpenes, isolated from CH_2Cl_2 extract of *Potamogeton malaianus*, exhibited potent antiviral (HSV-1) activity (with IC_{50} values of 3-8 μg/mL). [106].

Antiprotozoal Activities (Antiplasmodial–Antileishmanial- Trypanocidal)

Extracts and labdane-type diterpenes from *Andrographis paniculata* showed anti-malarial activity of against *Plasmodium berghei* NK65 in *Mastomys natalensis* [146].

Bioguided fractionation of extracts of *Aframomum latifolium* and *A. sceptrum* (Zingiberaceae) resulted the isolation of several labdanes, which showed moderate *in vitro* activity against chloroquine-sensitive *Plasmodium falciparum* strain [147].

Six labdanes (**1**-**6**) compounds **1**-**6** as the labdanes pinusolide (**1**), pinusolidic acid (**2**), isocupressic acid (**3**), lambertianic acid (**4**), and the isomeric lactols **5** and **6,** four isopimaranes (**7**-**10**), including three new natural products (**7**, **9**, and **10**), were isolated from *Platycladus orientalis*(L.) Franco (Cupressaceae) Fig. **11**. Compounds **1**-**9** and aframodial (**11**) were tested for their *in vitro* antiplasmodial activity and for their ability to induce changes of erythrocyte shape in order to obtain data about possible correlation between the two effects. All compounds tested exhibited weak (IC_{50} > 25 μM) *in vitro* antiplasmodial effects against *Plasmodium falciparum* strain 3D7. At the same time, the compounds caused echinocytic or stomatocytic changes of the erythrocyte membrane curvature, indicative of their incorporation into the lipid bilayer, in the concentration region where the antiplasmodial activity was observed [148].

In the search for new leishmanicidal agents, the neutral extract of the stem bark of *Polyalthia macropoda*

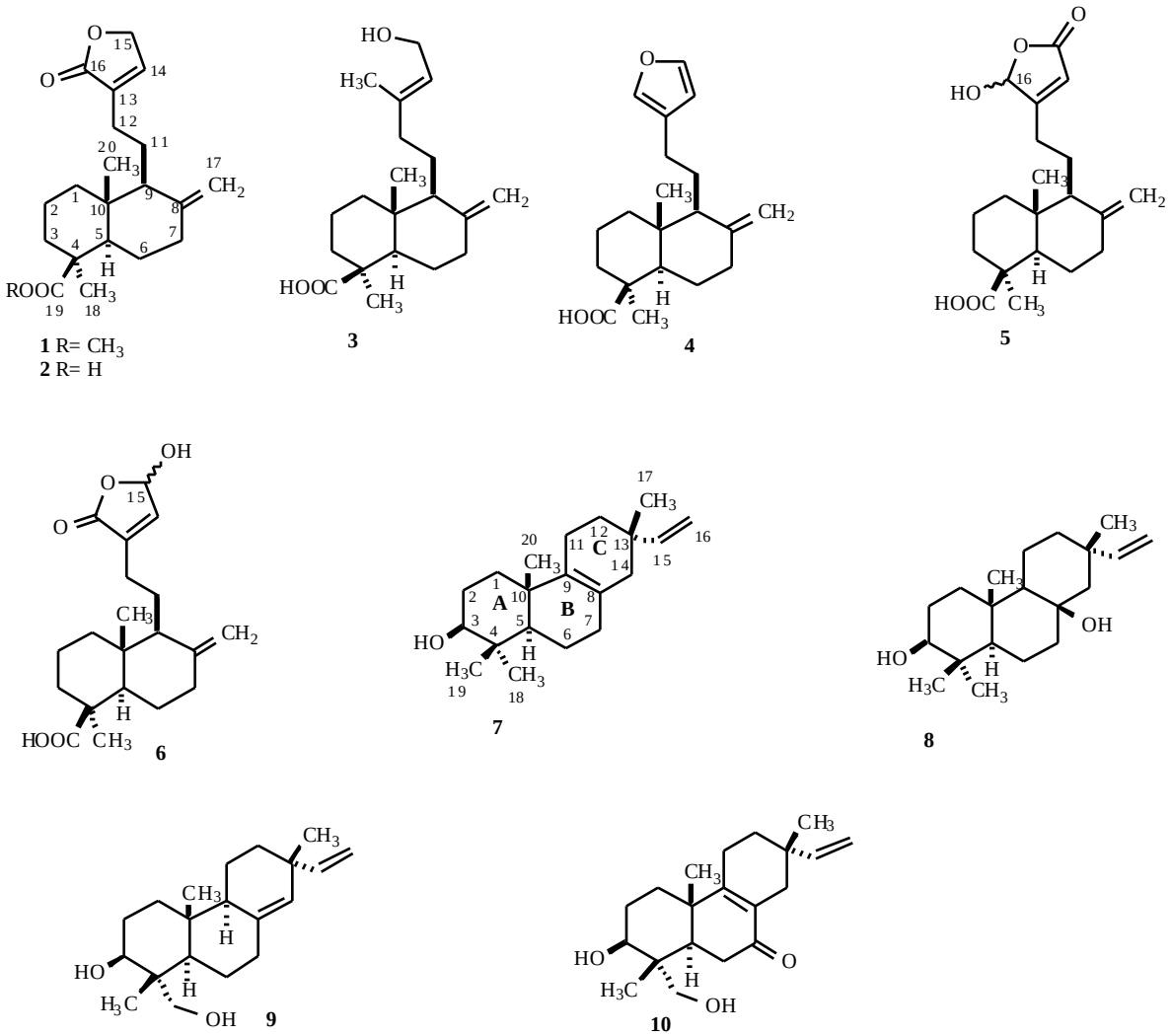


Fig. (11). Labdanes from *Platycladus orientalis*.

(Annonaceae) was subjected to *in vitro* bioassay on cultures of *Leishmania donovani*, a visceral leishmaniasis agent. The exhibited activity has been related to the existence of a labdane diterpene, which at a concentration of 0.25mg/ml, inhibits the parasites cell division to an extent of 15% complete inhibition [149].

Several ent-manoyl oxides obtained from natural products (Andalusian *Sideritis* species) through chemical and microbiological procedures, as well as a series of labdans and their derivatives were tested *in vitro* as novel potential antileishmanial drugs using an *in vitro* test system against extracellular promastigotes and intracellular amastigotes of *Leishmania donovani* in murine macrophages [150-154].

Labdane type diterpenes from *Alomia myriadenia* (Asteraceae) showed trypanocidal activity. They tested *in vitro* against *Trypanosoma cruzi* in infected murine blood, and caused lysis of 100% of the parasites at 250 µg/ml [144].

ACTIVITIES OF LABDANE-TYPE DITERPENES ON ENZYME SYSTEMS

Inhibitors of Adenosine Transferase

From the marine orange sponge *Agelas mauritiana*, agelasimine A and B showed an effect on the smooth muscle relaxation of rabbit gut and bovine coronary artery was studied and both caused relaxation in the tissue (ED_{50}=3-10µg/ml). Nucleoside transport into rabbit erythrocytes (IC_{50}=6-14µg/ml) was inhibited by agelasimine A and B. Both the compounds acted as α-adrenergic blockers and as Ca^{2+} channel antagonists [35, 68].

Inhibitors of Aldose Reductase

Accumulation of sugar sorbitol formed from D-galactose by aldose reductase enzyme results in the appearance of cataract of the lens of eyes in galactosemic patients. Due to the increasing therapeutic demand new inhibitors of aldose reductase are needed. From the marine sponge *Dysidea* sp. some metabolites inhibiting the activity of enzyme aldose reductase were isolated. The active principle isolated was dysideapalaunic acid with a labdane unit [32, 33, 68].

Adenylated Cyclase Enzyme System (AC)

Manoyl oxide and forskolin can activate adenylated cyclase enzyme system (AC), while other derivatives of manoyl oxides, naturally occurring, semi and/or synthetic or biotransformated by the microorganisms *Curvularia lunata* exhibit comparable bioactivities [15, 156].

Protein Kinases

Forskolin has been shown that can control protein kinase A (PKA) and protein kinase B (PKB) [157,158,159].

Inhibitors of Phospholipase A_2

Hallisulphate isolated from the dark brown sponge *Halichondriidae*, exhibiting as it has been referred above antifungal and antibacterial activity, also showed 100% inhibition of the enzyme phospholipase A_2 (PL A_2) at a concentration of 16µg/ml [34, 68]. A natural labdane isolated from the plant *Sideritis javalambrensis* also inhibits non-pancreatic secretory PL A_2 and human secretory synovial PL A_2. The importance of this activity is that PL A_2 catalyzes the hydrolysis of phospholipids esterified at the second carbon in the glycerol backbone, as arachidonic acid is like that commonly esterified and the action of PL A_2 releases arachidonic acid for metabolism *via* the cyclooxygenase and lipoxygenase pathways [160,161].

INHIBITORS OF SUPEROXIDE ANION RADICAL RELEASE

Some derivatives of agathic acid, including the 19-*nor* alcohol, have been isolated from *Agathis lanceolata* (Asteraceae) and appeared as inhibitors of superoxide anion radical release [162]. *Cistus monspeliensis* (Cistaceae) showed a significant inhibition of lipid peroxidation in rat liver micrsomes and a dose-dependent free-radicalscavenging capacity [163].

β-Glucuronidase Inhibitor

The extract of the tropical Paraguayan plant drug *Scoparia dulcis* (Scrophulariaceae) well-known in traditional medicine as Typycha Kuratu has been reported to inhibit the activity of β-glucuronidase. Three labdanes have been isolated and identified from the plant (scoparic acids (A-C) all of them but mostly scoparic acid A exhibited a strong inhibition of β-glucuronidase, comparable to that of glucosaccharo-1,4-lactone (an experimental β-glucuronidase inhibitor) [164-166].

Reduction by Arachidonic Acid of Prostaglandin i_2-Induced Cyclic Amp Formation Involvement of Prostaglandins E_2 and $F_{2\alpha}$

Arachidonic acid reverses the increase in cyclic AMP levels of washed human platelets exposed to prostaglandin (PG)I_2, under conditions where the PGH_2 analogue U46619 is ineffective. This effect of arachidonic acid was inhibited by aspirin, a cyclooxygenase inhibitor but not by the thromboxane (Tx) synthase inhibitor Ridogrel, which induces by inhibiting the conversion of PGH_2 into TxA_2, an overproduction of PGE_2, PGD_2 and $PCF_{2\alpha}$. Addition of PGE_2 or $PGF_{2\alpha}$, which share a receptor with PGI_2 to washed human platelets also induced a decrease in cyclic AMP levels but PGD_2, which interacts with a different receptor had no effect. Thus, neither PGD_2, PGG_2, PGH_2, TxA_2, nor TxB_2, formed from arachidonic acid *via* the cyclooxygenase pathway is involved in the decrease in cyclic AMP levels. These findings were confirmed using forskolin, a diterpene from the labdane family, which enhanced the formation of cyclic AMP synergistically with the PGs [167].

NATURAL SWEETENING AGENTS

There are several sweetening agents available for people suffering from diabetes, for example, the sodium salt of saccharin. The plants that demonstrate hypoglycemic effects

within the body play a major role in folk medicine. Such compounds have been isolated from *Baccharis gaudichaudiana* (Asteraceae) [168].

A steviol bisglucoside (rubusoside) is the sweet principle of a Chinese *Rubus* species (Rosaceae), which was tentatively identified as *Rubus chingii* Hu. Examination of a Japanese plant that had also been correctly identified as *R. chingii*, but was not sweet, afforded a series of *ent*-labdane glucosides, these were named the goshonosides F1-F5. The original Chinese plant was recognised to be a different species and was renamed *Rubus suavissimus* S. Lee [169].

Saudin is a novel 6,7-secolabdane, which possesses hypoglycaemic properties and has been isolated from *Cluytia richardiana* (Euphorbiaceae). Further more saudin was found to possess a significant hypoglycemic effect in nonalloxanized, rather than alloxanized fasting mice [170,171]. Extracts of *Stevia rebaudiana*, which contain the *ent*-kaurene glycoside stevioside, are used as a sweetening agent while the plant also contains some antihyperglycaemic constituents. In the search for these, some *bis-nor*-diterpenoids the sterebins A-D were isolated [172].

Abortifacient Activity in Cattles and Sheeps

Plant induced abortions are significant poisonous plant problem worldwide from ponderosa pine needle-induced abortions and Monterey cypress (*P. ponderossa* and *Cupressus macrocarpa*). A crude acid fraction isolated from the needles of *Pinus ponderosa* Laws) induced abortions when fed to late-term pregnant beef cows. The major components identified in this abortifacient fraction were two labdane diterpene acids, imbricataloic and isocupressic acids. From this crude acid fraction, isocupressic acid was isolated and dosed by gavage to five pregnant cows starting on day 250 of pregnancy. Four of the five cows aborted calves when administered isocupressic acid at dosages between 99 and 152 mg/kg (twice daily). At a lower dosage of 66 mg/kg no abortion occurred. The primary abortifacient constituent in ponderosa pine is isocupressic acid, while imbricataloic acid may also be an active component based on a labdane structure very similar to that of isocupressic acid. A comprehensive study of structure / activity relationships between labdane type diterpenes and abortifacient activities is under examination [173,174]. Also, two esters of iscupressic acid, acetylisocupressic and succinylisocupressic acid also occur in ponderosa pine needles, but their abortifacient activity has been attributed to the hydrolysis of the simple ester linkage in the rumen of the cow to yield additional isocupressic acid. The existence of isocupressic acid in *Cupressus macrocarpa* helped to establish the aetiology of macrocarpa-induced abortions in New Zealand. Isocupressic acid was first characterised after isolation from *Cupressus sempervirens*, while it has also been found in *Calocedrus formosana*, *Cryptomeria japonica*, *Pinus sibirica*, *P. armandii*, *Juniperus chinensis*, *J. communis*, *Phyllocladus trichomanoides*. Isocupressic acid was also detected in 14 other species among selected North American gymnosperms, in addition to ponderosa pine it has been detected with significant levels being found in Jeffrey pine (*Pinus jeffreyi*), Lodgepole pine (*P.contorta*), Rocky mountain juniper (*Juniperus scopulorum*) and common juniper (*Juniperus communis*) while the southern pines *P. echinata*, *P. taeda*, *P. palustris*, *P.elliotti* and the *Abies* contain low or undetectable levels of isocupressic acid [175].

The effects of isocupressic acid (ICA) [15-hydroxylabda-8 (17), 13E-dien-19-oic acid], from *Pinus ponderosa*, *Pinus contorta*, *Juniperus communis* and *Cupressus macrocarpa*, have studied on bovine oocyte maturation (*in vitro* maturation (IVM)—Experiment I) and preimplantation embryo development (*in vitro* culture (IVC)—Experiment II) using *in vitro* embryo production techniques were tested. Results from Experiment I and II indicated that ICA neither inhibit oocyte maturation nor adversely affect preimplantation embryo development. In conclusion, ICA showed no adverse effects on oocyte maturation and preimplantation embryo development *in vitro* or subsequent viability *in vivo* using the ICA concentrations and *in vitro* culture parameters of this study [176].

Anti-Hypertensive Activity

Coleus forskohlii (Lamiaceae) has played an important role in Hindu and Ayurvedic traditional medicine and over the last few years a component, forskolin, has been attracting considerable interest because of its anti-hypertensive activity [21,177].

Hepatoprotective Activity

Andrographis paniculata (Acanthaceae), commonly known as Kalmegh, is widely used in the traditional system of Indian Medicine in the treatment of hepatitis. The plant is reported to possess protective activity against various liver disorders, mainly due to its labdane-type diterpenes [178-182].

The labdane-type diterpenes isolated from the MeOH extract from Brazilian propolis exhibited significant hepatoprotective activity when they were tested on D-galactosamine (D-GalN)/tumour necrosis fact or-alpha (TNF-alpha)-induced cell death in primary cultured mouse hepetacytes [49].

Anti-Inflammatory Activity

The isolation of a number of manoyl oxide derivatives from *Sideritis javalabrensis* (Lamiaceae) has been reported. The hexane extract of the plant as well as the isolated ent-16-hydroxy-13-epimanoyl oxide showed strong anti-inflammatory activity [183]. Two purified plant products were obtained from anti-inflammatory extracts of the Spanish herb *Sideritis javalabrensis: ent*-13-*epi*-12 alpha-acetoxy-manoyl oxide (manoyl oxide F1) and *ent*-8-alpha-hydroxy-labda-13(16), 14-dien (labdane F2). They were evaluated for possible anti-inflammatory actions *in vitro*, and were compared with aspirin, sodium salicylate and indomethacin. Neither of the natural products affected superoxide generation or scavenging nor they affect granular enzyme secretion from activated human and rat neutrophils. The compounds were not toxic to the cells at up to 10^{-4} M. However, both of them inhibited thromboxane B-2 and leukotriene B-4 generation by A23187-treated rat peritoneal leukocytes,

suppressing leukotriene generation at 10^{-5} - 10^{-4} M and thromboxane B-2 at 10^{-4}. Labdane F2 also inhibited human secretory synovial phospholipase A(2) activity at 10^{-3} M, a property not shared by manoyl oxide F1. These two natural products interact, with the eicosanoid system, perhaps at the phospholipase level, but do not interfere with the other tested leukocyte functions or with reactive oxygen species, and are non-toxic at the doses used [161, 184].

Cryptomeria japonica (Taxodiaceae) is been traditionally used in Japan against wound eczemas, and also for its anti-inflammatory activity [185], while three new labdane-type diterpenes named hedychilactones A-C (Fig. **12**) were isolated from the fresh rhizome of *Hedychium coronarium* Koenig.(Zingiberaceae) and were found to inhibit the increase of vascular permeability induced by acetic acid in mice and nitric oxide production in lipopolysaccharide-activated mouse peritoneal macrophages [115, 186, 187].

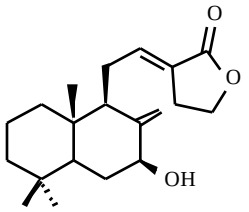


Fig. (12). Hedychilactone A.

Andrographis paniculata, is shrub belonging to the Acanthaceae family commonly called "Kalmegh" in India. The plant is valued by the local people as a medicine for the treatment of a variety of diseases. Herbaria collections from the Botanical Dept, National Museum, Manilla, recorded that the plant is of Chinese origin and known as "Alui" [188]. "Alui" is one of the world's most important medicinal plants used in Chinese and Ayuverdic medicine for gastric disorders, colds, influenza and other infectious diseases, the extract of the plant also called "Kan Jang" was developed by the Swedish Herbal Institute and used in Scandinavia for the common cold. Clinical studies conducted elsewhere indicate that the plant is of help in epidemics. During the influenza epidemic of 1919 in India, a tincture of the plant was said to have arrested the epidemic spread. Since *Andrographis paniculata* was able to inhibit the growth of *S. aureus, P. aeruginosa, P. vulgaris, Shigella dysenteriae* and *E. coli* it was recommended for the treatment of different diseases ranging from bacterial dysentery, gastrointestinal disorders, tonsillitis, pneumonia, pyelonephritis to abscesses. The extract of the plant has been demonstrated to be effective for the treatment of pharyngotonsillitis in adults. The clinical findings require further validation using rigorous testing were associated with the stimulation of both specific and nonspecific immune response and its antiviral activity. Andrographolide and related compounds have been investigated for their pharmacological activities in several animal's studies, showing antipyretic and anti-inflammatory activity in animals with experimentally induced fever edema and inflammation. The anti-inflammatory effect of andrographolides disappeared in adrenal-ectomized animals. High dosage of the andrographolides caused thymic atrophy in young mice suggesting a possible involvement of the pituitary and adrenal systems [189]. It was shown that andrographolides reduce the intensity of the peritoneal inflammation produced by acetic acid in mice, indicating its ability to inhibit the permeability of small blood vessels. Andrographolide, at real dose up to 300 mg/kg was very tolerated both after acute or sub-acute and chronic models of inflammation, without side effect on gastric mucosa. The anti-inflammatory mechanism of action is supposed to be different from that of conventional anti-inflammatory drugs. It has been showed how andrographolide affects the most important inflammatory mediators, such as eicosanoids and platelet activating factor (PAF). Inhibition of the biosynthesis of eicosanoids is characteristic for NSAID, while PAF antagonists are used as potential agents in inflammation, asthma, cardiac anaphylaxis, thrombosis, gastrointestinal ulceration, endotoxic shock and allergy. In isolated human polymorphonuclear leukocytes (PMNL) no influence on the biosynthesis was found, it could be shown that andrographolides inhibit PAF-induced human blood platelet aggregation in dose dependent manner. These results indicate that andrographolides have a mechanism of action different from that of non-steroidal anti-inflammatory drugs (NSAID) and most likely associated with the cardiovascular and antithrombotic activity described of *Andrographis paniculata*. Several controlled clinical studies in common cold have been performed as pilot trials to the *Andrographis paniculata* dried extract [190, 191].

Immune System

Forksolin has been showed as ability to alter human peripheral blood lymphocyte activation by antigens while it also interferes with the production of interleukins. Forskolin influences also on B-lymphocytes; the cells responsible for the production of immunoglobulins, while forskolin mainly inhibits T cell proliferation, a labdane from *Leonurus heterophyllu*s (Lamiaceae) has been reported to induce proliferation of this T cell lymphocyte subpopulation [69, 192-194].

Anti-PAF Activity

Pinusolide, a labdane type diterpene lactone isolated from ex. *Biota orientalis* and now renamed *Platycladus orientalis* (Cupressaceae) was found to be a potent platelet activating factor (PAF) receptor binding antagonist. To investigate the structure-activity relationship and find derivatives with improved pharmacological profiles, 17 pinusolide derivatives were prepared and tested for their ability to inhibit the PAF receptor binding. The results demonstrated that the carboxymethyl ester group at C-19, the integrity of the alpha, beta unsaturated butenolide ring, and the exocyclic olefinic function of pinusolide are all necessary for its maximum PAF receptor binding inhibitory activity [195-198].

The 90% methanol-soluble fraction of a Bhutanese medicinal plant Shug Chher, tentatively assigned to *Juniperus communis*, (Taxodiaceae) exhibited inhibition of platelet aggregation induced by platelet activating factor. Bioassay-directed fractionation led to the isolation of eight labdane-diterpenoids, which also inhibited platelet aggregation [199].

Endocrine Effects

Forsklin also exhibits activation to almost all hormone-sensitive adenylate cyclase, while semisynthetic labdanes affect the release of adenohypophysial hormones, prolactin (PRL), somatotropin (STH), and adrenocorticotropic hormone (ACTH)[200].

A study conducted on prepubertal male rats showed that chronic administration (60 days) of a *Stevia rebaudiana* (Asteraceae) aqueous extract produced a decrease in final weight of testis, seminal vesicle and cauda epididymis. In addition, the fructose content of the accessory sex glands and the epididymal sperm concentration are decreased. *Stevia* treatment tended to decrease the plasma testosterone level, probably by a putative affinity of glycosides of extract for a certain androgen receptor, and no alteration occurred in luteinising level. These data are consistent with the possibility that *Stevia* extracts may decrease the fertility of male rats [201].

Insect Anti-Feedant Activity

Some labdanes (grindelane diterpenoids) obtained from *Grindelia humilis* (Asteraceae) have shown aphid-deterrent activity whilst *G. camporum*, *G. paludosa* and *G. stricta* are also sources of compounds of the same activity. Several hemisynthetic derivatives of these compounds as well as derivatives received after biotransformation of grindelic acid by *Cunninghamella echinulata*, have also been exhibited similar activities [202-207]. As part of search for natural insecticides, some labdanes from *Isocoma tenuisecta* (Asteraceae) have also showed activities [208]. *Hyptis spicigera* (Lamiaceae) is been used for its anti-insect activity, as seven new labdane type diterpenes with insecticidal properties were isolated from the aerial parts of the plant. Almost all of them significantly inhibited larval growth of the European corn borer [209]. The furanoid labdane type diterpenes, from *Potamogeton malaianus* were showed to possess cytotoxicity toward insect cells (fall armyworm and mosquito larvae from 11-72 μg/ml [106].

Sclareol is a strong inhibitor of the growing of plants and inhibits the fungi of psoriasis, as well as inhibits the growth of wheat coleoptile and reduces the severity of rust infection in French bean [210-212].

The extracts of the bark from *Juniperus procera* (Cupressaceae) is used as potential anti-termite natural pesticide, while labdane-diterpenoids from the cones of *Chamaecyparis obtusa* (Cupressaceae) exhibited antifeedant activity against the pest insect *Spodoptera litura* [213, 214].

Anti-Algal, Phytotoxic Activities

Twenty labdane-diterpenes isolated from the aquatic plants *Ruppia maritima* and *Potamogeton natans* (Potamogetonaceae) were tested to detect their effects on aquatic organisms from different trophic levels. Toxicity tests were performed on aquatic producers (the alga *Selenastrum capricornutum)* and consumers including a rotifer (*Brachionus calyciflorus*), a cladoceran (*Daphnia magna*) and two anostracan crustaceans (*Thamnocephalus platyurus*, and *Artemia salina*) the furano-ent-labdanes exhibited high toxicity toward all of these organisms while the rest had high toxicities towards the algae and the rotifers and were inactive for the crustaceans [215, 216].

Furano-*ent*-labdanes from the aquatic plant *Potamogeton natans* and *Potamogeton pectinatus* showed *in vitro* phytotoxicity against *Raphidocelis subcapitata*, a microalga used in aquatic tests [217].

Several labdanes from the aerial parts of *Xanthocephalum gymnospermoides* var *eradiatum* (Asteraceae) caused significant inhibition of the radicle growth of seedlings of *Amaranthus hypochondriacus* [218, 219].

PERFUMERY-SPICES

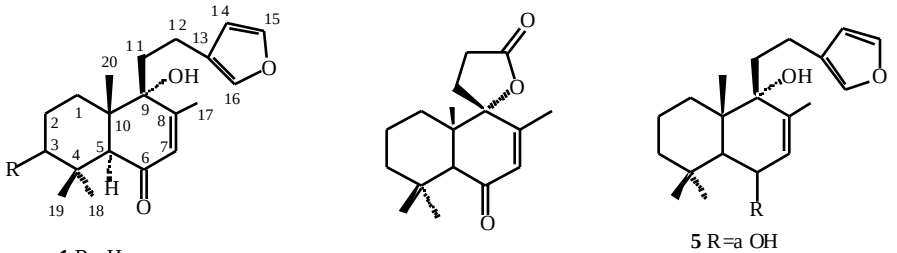
Alpinia galanga is a plant used for flavouring purposes. Its pungent taste is associated with labdane diterpenoids galanal A and B [220]. The hot-tasting dialdehyde is amongst the constituents of the seeds of *Aframomum daniellii* (Zingiberaceae), [221] which are used as a condiment. *Copaiba* oil, which is a mixture of oleoresins extracted from *Copaifera* L. (Leguminosae) species and used for medicinal and cosmetic purposes, has been shown to contain several classes of diterpenoids among which are labdanes [222-224]. Structures of compounds that are used in the perfumery product Ambrox have been described whilst the degradation of dimethyl agathate to norlabdanes of the ambergris type has been reported. Conformation-odour relationships in the Ambrox analogues have been explored [225-227].

VARIOUS

The structure of the lactone phlogantholide A, which was obtained from the Indian Medicinal plant *Phlogacanthus thyrsiflorus* (Acanthaceae), has been established. It is interesting to notice that the plant is used to treat bronchial conditions- a similar use has been reported for *Andrographis paniculata* which contains the related andrographolides [228].

The structure-hemostatic activity relationship of the labdane-diterpene lagochilin from *Lagochilus hirsutissimus*, (Lamiaceae) and its natural and synthetic derivatives was investigated [229].

Cardiotonic activity has been exerted from labdane diterpenoids (medigenin, medigenin acetate and medinin) from *Melodinus monogynus* (Apocynaceae). All the three compounds showed cardiotonic activity with (a) isolated frog heart perfused with ringer solution and (b) isolated mammalian (rabbit) heart perfused with ringer-Locke's solution isolated by Anderson-Coronary apparatus. On the isolated frog heart, medigenin increased the tone and force of contraction of the heart and the heart rate was decreased. Similarly appositive inotropic and negative chronotropic effect was observed on the isolated rabbit heart. The acetylated derivative also increased the tone and force of myocardial contraction and decreased the heart rate. Medinin showed no cardiac activity with either of the heart preparations [230]. The extract (chloroform-methanol 1:1) of the plant *Dodonaea viscosa* (Sapindaceae) resulted in the isolation of labdane-diterpenes, which elicited a



1 R = H
2 R = aOH
3 R = bOH

4

5 R = a OH
6 R = a OAc
7 R = b OH

Fig. (13). Structure of Solidagenone **1** and its derivatives **2**–**7**.

concentration-dependent inhibition of the spontaneous and electrically induced contractions of guinea-pig ileum. In addition, these substances were capable or relaxing contractions or rat uterus induced by Ca^{2+} in K+ depolarizing solution, displacing to the right the concentraton response curves to Ca^{2+}. These results suggest that the diterpene produces an interference with calcium metabolism in smooth muscle cells. The spasmolytic activity exhibited by the active principle from *D. viscosae*, provides the pharmacological basis for the traditional use of the plant as an antispasmodic agents Analgesic, anti-pyretic and anti-ulcerogenic effects of *Andrographis paniculata* [231-234].

Leonotinin a labdane diterpenoid which was obtained from *Leonotis nepetaefolia*, a plant used for treating skin infections exhibited similar activities[235]. In Thibet, the roots of *Phlomis younghusband* and *P. medicinalis* are used against cough and fever [236]. Derivatives of sclareol, have been exhibited antihypoxic effects in mice and also induced changes in core body temperature by interacting with dopamine receptors, during *in vivo* experiments in rats [68, 237-239].

From *Solidago canadensis* (Asteraceae), it has been firstly isolated the labdane diterpene solidagenone 1. 1 and its semisynthetic and biotransformations products 2–7 Fig. (**13**) were assessed for gastroprotective effect in the HCl·EtOH-induced lesions in mice. At 100 mg/kg, solidagenone presented a statistically significant gastroprotective effect ($P<0.05$) comparable to lansoprazole at 20 mg/kg [240].

Glycosides of *Stevia rebaudiana* (Asteraceae) leaves, as stevioside, as it has been already referred are powerful sweetening agents, and have been used for the last 15 years by Brazilian people for this purpose. Physiological and pharmacological experiments have suggested that stevioside and *Stevia rebaudiana* extracts promote effects on some physiological systems, such as cardiovascular and renal [241].

It has been studied the effects of *Stevia rebaudiana* extract on cardiovascular parameters in humans reported that this extract induce hypotension and marked decrease in heart rate. This finding was confirmed by another author, following the stevioside administration in rats. In addition, stevioside and *Stevia* extracts are able to induce diuresis, natriuresis and kaliuresis. The hypoglycemic effect reported by some authors has been observed exclusively with total extracts of *Stevia rebaudiana a*nd not with purified stevioside [242, 243]. The effects of crude extract of *Stevia rebaudiana* on renal water and electrolytes excretion have been studied; during the intravenous infusion of the extract (0.05 mg/min/100g) no significant differences were detected in mean arterial pressure or renal haemodynamics parameters. In contrast, fractional water and sodium excretion and solute clearance increased significantly, in both groups of animals. In antidiuresis rats the extract significantly increased reabsorption of water by collecting duct and in water diuresis animals the extract significantly increased free water clearance. The data suggest preferential action of the extract in the proximal tubular cells involved with salt transport mechanism [244, 245].

CONCLUSION

Labdane type-diterpenes exhibit a broad spectrum of significant biological activities. The scope of this report was to underline the role of these compounds not only through their activities but also as potential pharmacological agents.

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