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(+)-LARIXOL AND LARIXYL ACETATE: SYNTHESES, PHYTOCHEMICAL STUDIES AND BIOLOGICAL ACTIVITY ASSESSMENTS

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Abstract. (+)-Larixol and larixyl acetate are well known labdane-type diterpenoids widely used in organic synthesis. The chemistry of (+)-larixol had a slower evolution compared to other diterpenoids and the peak of its heyday can be considered the 2000s. During this period, the most important works describing the syntheses based on (+)-larixol and its acetate appeared, some of them being mentioned in reviews devoted to diterpenes. So far, however, no review has been published dedicated exclusively to chemistry of (+)-larixol and larixyl acetate, neither phytochemical investigation of sources containing these compounds nor their biological activity study. The present review seeks to cover and fill in the gaps regarding these topics based on available scientific data published after the 2000s.

Keywords: (+)-larixol, larixyl acetate, synthesis, chemical composition, biological activity.

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List of abbreviations and notations:

1D, 2D	One-dimensional and two-dimensional
NMR	Nuclear magnetic resonance
2,4-DNPH	2,4-Dinitrophenylhydrazone
AcCl	Acetyl chloride
ASE	Accelerated solvent extractor
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EC_{50}	Half maximal effective concentration
EO	Essential oil
EtOH	Ethanol
FT-IR	Fourier transformation infrared spectroscopy
FT-NIR	Fourier transformation near-infrared spectroscopy
FT-RAMAN	Fourier transform Raman spectroscopy
GC-MS	Gas chromatography-mass spectrometry
GC-FID	Gas chromatography-flame ionization detection
HD	Hydro-distillation
HE	Hexane
HR-LC/ Q-TOF/MS	High resolution-liquid chromatography/Quadrupole-time- of-flight/Mass spectrometry
IC_{50}	Half maximal inhibitory concentration
KOAc	Potassium acetate
LAH	Lithium aluminium hydride
LC_{50}	Lethal concentration 50
LIRE	Lung ischemia-reperfusion edema
MEAIL	Methanolic extract from *Acalypha indica* L. leaves
MFC	Minimal fungicidal concentration
MIC	Minimum inhibitory concentration
MIZ	Maximum inhibition zone
MMT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MPFA	Monoperftalic acid
NBS	*N*-Bromosuccinimide
OECs	Oil extractives components
SC-CO_2	Supercritical carbon dioxide
S_N2	Bimolecular nucleophilic substitution
TBI	Traumatic brain injury
THF	Tetrahydrofuran
$TMSCHN_2$	Trimethylsilyldiazomethane
TOF/MS	Time of flight-mass spectrometry
TRPC3	Transient receptor potential canonical 3 activity
TRPC6	Transient receptor potential canonical 6 activity
TRPC7	Transient receptor potential canonical 7 activity

Introduction

The chemistry of (+)-larixol (**1**) began with the isolation of its acetate **2** from the oleoresin of European larch (*Larix decidua* Mill.), followed by the saponification of the latter [1]. In the 70s, several groups of researchers contributed to the identification of the absolute configuration of (+)-larixol (**1**) as 13-(*S*) [2-8]. In the following two decades, both compounds were identified in various species of larch (*Larix sibirica* Labd.,

Larix decidua Mill., *Larix gmelini* Rupr.) and hybrids (*L.* x *eurolepis* Henry, *L. decidua* x *L. kaempferi*) [9-11].

In terms of organic synthesis, (+)-larixol (**1**) and its acetate **2** surpass other labdane diterpenoids due to the C-6 hydroxyl group. Over the years, various chemical transformations were performed selectively or on both hydroxyl groups, or by modifying the side chain [4-7]. At the same time, a special interest of researchers was focused on an oxidative transformation of compounds **1** and **2** [7,12-21]. In addition, a research paper on microbial transformation of (+)-larixol (**1**) and its derivatives was reported by Herlem, D. *et al*., who performed the microbial hydroxylation by *Mucor plumbeus* LCM, which led to C-2 hydroxylated products [21].

As well as other easily accessible diterpenoids, (+)-larixol (**1**) and its acetate **2** were widely used for the preparation of biologically active drimane sesquiterpenoids or fragrant compounds. These syntheses were described in several reviews, as separate compartments [22-25]. The traditional synthetic pathways based on compounds **1** and **2** include successive oxidative degradation of their side chains. For this, efficient methods have been developed using various oxidizing agents [19,21,26] or their combination with Norrish II type photochemical degradation of intermediate methyl ketones [27]. All these efforts have yielded formidable results known today as synthesis of some natural drimane-type sesquiterpenoids such as (-)-drimenol, (-)-uvidin C, (-)-albrassitriol, (-)-*epi*-albrassitriol, (+)-6-ketoeuryfuran, (+)-6-ketowinterin, and (-)-7-ketoeuryfuran, pereniporin B and (-)-cinnamosmolide [28-31], natural labdane diterpenoid crotonadiol and its isomer [32], Ambrox®-like compounds including Δ^5-ambroxene, Δ^6-ambroxene, 6*α*-hydroxy ambrox and 6-oxo ambrox [25,33,34], ambra oxide related compounds [25,35] and a series of labdane furanes such as hedychenone, yunnancoronarins A and D [25,36].

The review is designed for interested researchers in the field, aiming to present them recent scientific achievements, those partially cited or omitted previously in the fields of chemistry, phytochemistry and biological activity of (+)-larixol and larixyl acetate.

Background

Recent progress in chemistry and phytochemistry of (+)-larixol and larixyl acetate

Most of the syntheses mentioned above are based on the oxidative breakdown of the C-9 side chain of (+)-larixol (**1**) or its acetate **2** leading to a wide variety of synthons, including 14,15-bisnorlabdene-13-ones **3**-**5**. The next transformations into target drimanes consist of multi-step procedures and this strongly influences their overall yields. For this reason, Vlad, P. *et al.* used the Norrish II type photochemical degradation of methyl ketones **3**-**5** (Figure 1) [27]. The results regarding the major reaction products were published in some reviews, whilst those regarding minor products were omitted [37].

In such a way, minor compounds **7**, **9** and **11** with unexpected bi- and tricyclic structure were isolated from the Norrish II reaction products (Scheme 1). Their structures were confirmed by 1D and 2D NMR analysis and single crystal X-rays diffraction. The compound **7** had a 6*α*-acetoxy-9,13*β*-epoxy-13*β*-methylpodocarpane skeleton and was obtained in ~4% yield, calculated on converted 6-acetoxy ketone **3**. Vlad, P. *et al.* proposed the probable way of its formation as a product of ketone **3** cyclization under UV-irradiation *via* intermediate state **6** (Scheme 1) [27].

Unlike that, compound **9** (~3%) is a product of the photochemical rearrangement and cyclization, as depicted in Scheme 1, which led to a tricyclic skeleton with a condensed cyclopentane ring (Scheme 1).

The most abundant was compound **11**, which was obtained in a 17% yield. Its 6*α*-acetoxy-8*β*,13,13,17-diepoxy-14,15-dinorlabdane skeleton was a result of ketalization, *via* intermediate state **10**, which occured in molecule of ketone **3** as result of photoexcitation and also of the addition of the residual oxygen from the reaction medium.

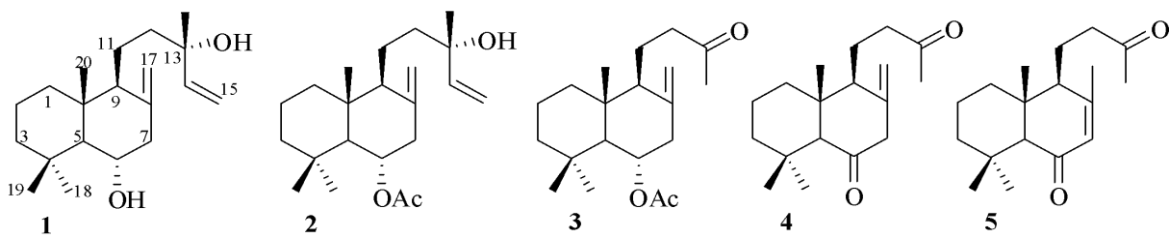


Figure 1. (+)-Larixol (1), larixyl acetate (2) and related dinorlabdane compounds 3-5 [27].

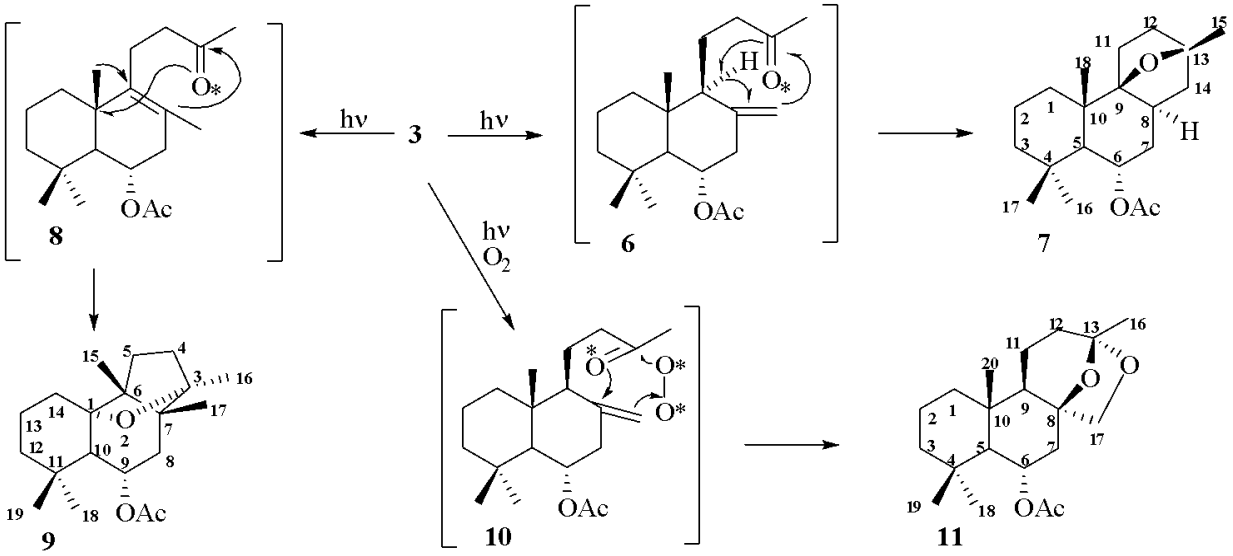
This fact was confirmed by additional reactions carried out under oxygen atmosphere, when compound **11** was obtained in 40% yield (Scheme 1). Their spectral data were in accordance with those of some related diastereomeric ketoketals reported before [7,14].

The minor compound **12** was isolated from the photochemical degradation product of methyl ketone **4** in a ~18% yield. The spectral data of liquid cyclobuto(18→6)-14,15-bisnorlabd-8(17)-ene-6-ol-13-one (**12**) were not enough for its structure characterization, for this reason an attempt was made to obtain the 2,4-dinitrophenylhydrazone derivative for the X-ray analysis. Surprisingly, a mixture of two 2,4-DNPH derivatives **13** and **14** was obtained, isolated and characterized due to acidic reaction conditions (Figure 2).

The one-step photochemical degradation of methyl ketones **3**-**5** led to the corresponding drimane dienes **15**-**17**, in good yields (36-76%) and variable conversion of the first (12-63%) as presented in Figure 2. In continuation, the dienes **15**-**17**, derived from (+)-larixol (**1**) were used as intermediates for regio- and stereoselective semisynthesis of some natural drimane sesquiterpenoids.

Starting from 6*α*-acetoxydiene **15** and following the same strategy of using non-conventional methods, Vlad, P. *et al.* [27] performed the synthesis of previously reported (±)-6-hydroxyeuryfuran (**18**) and (±)-6-ketoeuryfuran (**19**) [38] in enantiomeric pure forms, in ~75% and ~70% overall yields, and the first synthesis of drimanic anhydride (+)-6-ketowinterine (**20**), in ~53% overall yield (Figure 3).

To note that, the *meso*-tetraphenylporphyrin or eosine sensitized photooxidation was widely and efficient used by Vlad, P. *et al.* as a green chemistry method for the preparation of some intermediate endoperoxides, such as **21** and **22**, or anhydride **20** (Figure 3). Herein, the synthetic schemes were omitted because these were well-presented in a review published by Mahji, S. [37].



Scheme 1. The mechanisms of minor products 7, 9 and 11 formation under UV irradiation [27].

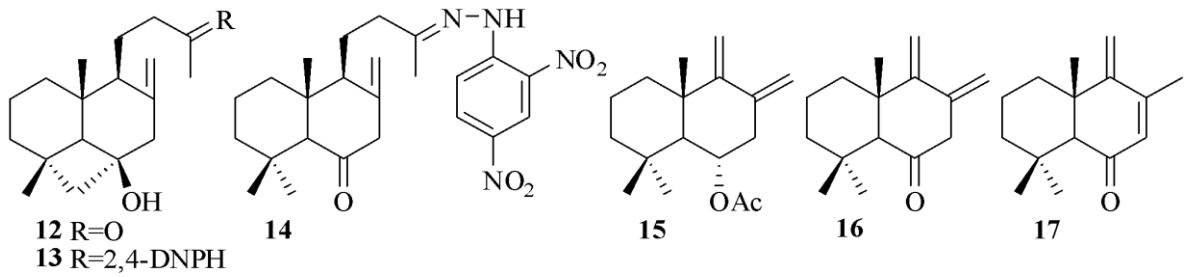


Figure 2. The minor 12-14 and major 15-17 products of Norrish II type reaction [27].

A successful attempt to synthesize fragrolide (**24**), a sesquiterpene lactone previously isolated from *Cinnamosma fragrance* [24], was described earlier [38]. To achieve this, the authors used the ketoperoxide **22**, which was reduced into triol **23** in depicted conditions (Scheme 2). Further oxidation of triol **23** with chromium trioxide led to mixture of ketoeuryfuran **19** and desired fragrolide (**24**), in ~32% and ~21% overall yield, recalculated for initial acetoxy diene **15**, that was much better than those previously published [39,40].

In turn, diene **17** was used as starting material for the synthesis of natural and biologically active drimanic compounds (-)-albrassitriol (**26**) and (-)-*epi*-albrassitriol (**27**) [41]. The first synthesis of these compounds from (+)-larixol (**1**) was reported by Lagnel, B. *et al.* in, 10- and 15-steps, ~8% and ~4% overall yields, respectively [28].

A much shorter synthesis includes an alternative two steps procedure of key intermediate ketodiol **25** preparation, by epoxidation of dienone **17** and $HClO_4$ assisted hydrolysis of resulting diastereoisomeric epoxides **28** and **29**. The reduction of ketodiole **25** with $LiAlH_4$ completed the synthesis of (-)-albrassitriol (**26**) and (-)-*epi*-albrassitriol (**27**) in ~12% and ~14% overall yields, respectively (Scheme 3) [30].

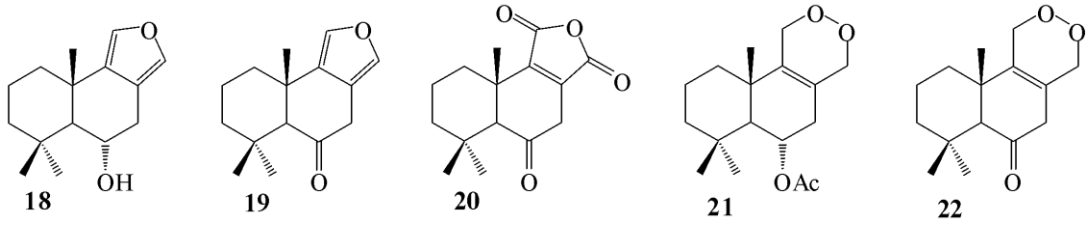
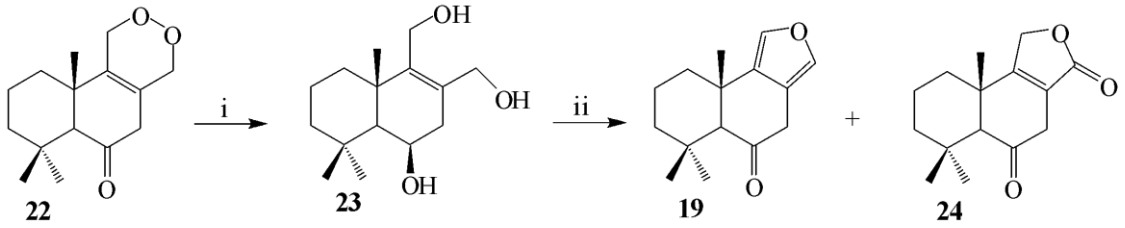
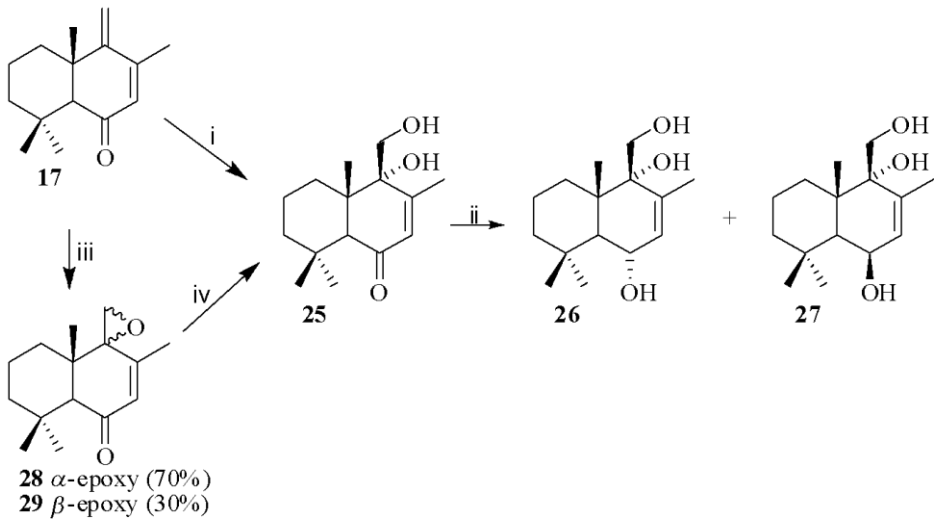


Figure 3. (+)-6-Hydroxyeuryfuran (18), (+)-6-ketoeuryfuran (19), (+)-6-ketowinterine (20) and intermediate endoperoxides 21 and 22 [29].



Reagents and conditions: (i) $LiAlH_4$, Et_2O (anh.), N_2, 2.5 h, r.t., 80%; (ii) CrO_3, Py, 4.5 h, r.t., 50% and 33%.

Scheme 2. Synthesis of fragrolide (24) starting from the intermediate endoperoxide 22 [39].



Reagents and conditions: (i) OsO_4, Py, 12 h, r.t., 91%; (ii) LAH, Et_2O, N_2, 0°C, 0.5 h, 44% and 48%; (iii) MPFA, Et_2O, 125 h r.t., 82%; (iv) $HClO_4$, THF, 49 h, r.t., 68%.

Scheme 3. Short synthesis of epimeric albrassitriols 26 and 27 [30].

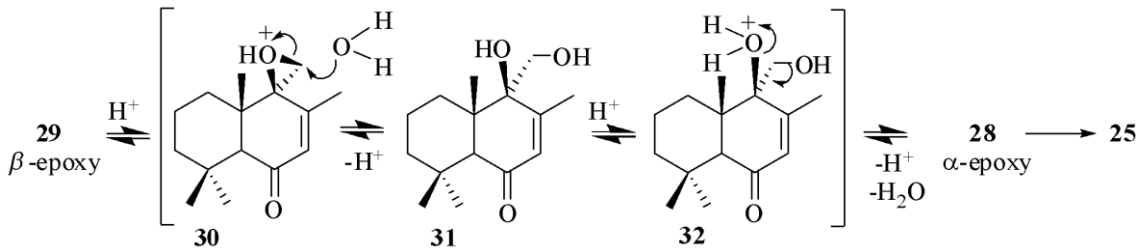
Vlad, P. *et al.*, explained the selective formation of ketodiol **25** from the mixture of epoxides **28** and **29** by two successive S_N2 substitutions during which a less stable *β*-epoxide **29** is interconverted into more stable *α*-epoxide **28** through intermediates **30**-**32** (Scheme 4) [30]. Such kinds of transformations are known and were reported before [42].

Based on the ketodiol **25**, formerly obtained from (+)-larixol (**1**) [30], the formal synthesis of pereniporin B (**38**) and cinnamosmolide (**39**) was performed [31]. The key step of this transformation is allylic bromination of C-12 methyl group from the ketoacetate **33** with NBS in CCl_4, which leads to bromide **34** (91%) (Scheme 5).

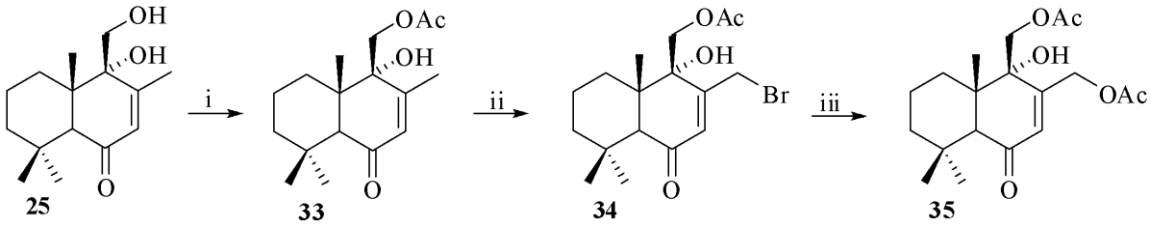
Herein, triole **36** was obtained by saponification of diacetate **35**, then it was oxidized with manganese dioxide into lactone **37** (Scheme 6). The transformation of lactone **37** into pereniporin B (**38**) was reported by Burke, S. *et al.* and included its reduction with DIBAL-H, followed by Fetizon's oxidation [40]. Cinnamosmolide (**39**) was prepared for the first time by acetylation of pereniporin B (**38**) in standard conditions [43]. Some of the intermediate from the Scheme 4 were synthesized from other sources and previously reported, *e.g.* triole **36** [44,45] and lactone **37** [46].

In contrast to the syntheses mentioned above, only several syntheses based on (+)-larixol (**1**) with conservation of the side chain are known [37-39], one of them being the synthesis of (+)-crotonadiol (**42**).

The history of the labdane diterpenoid labd-8(17),13*E*-dien-6*α*,15-diol (**42**) is quite long and confusing. For the first time it was synthesized by Haeuser, J. from larixyl acetate (**2**) [4]. The same product was obtained in a low yield by oxidation of larixyl acetate (**2**) with oxygen in the presence of heteropolyacids [47]. Both syntheses confirmed that diol **42** belongs to normal labdane enantiomeric series.

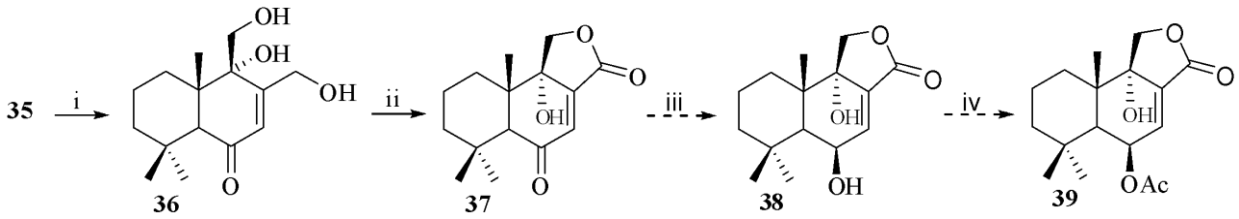


Scheme 4. The mechanism of epoxides 28/29 interconversion and ketodiol 25 formation [30].



Reagents and conditions: (i) Ac_2O, Py, r.t., 12 h, 86%; (ii) NBS, CCl_4, reflux, 9 h, 91%; (iii) KOAc, DMSO, r.t., 1 h, 98%.

Scheme 5. Polyfunctionalized intermediates 33-35 of formal synthesis of pereniporin B (38) and cinnamosmolide (39) [31].



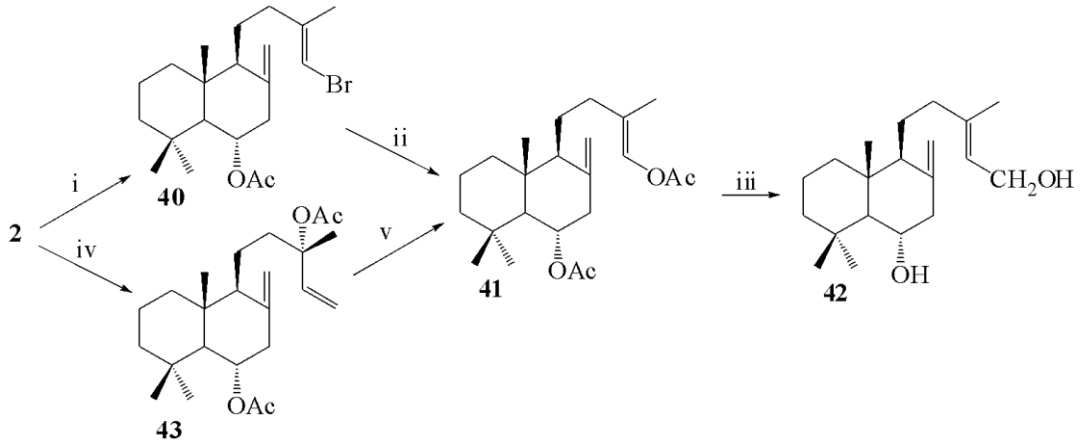
Reagents and conditions: (i) K_2CO_3, MeOH, r.t., 0.5 h, 99%; (ii) MnO_2, CH_2Cl_2, r.t., 70 h, 93%; (iii) performed by [44]; (iv) performed by [45].

Scheme 6. Formal synthesis of pereniporin B (38) and cinnamosmolide (39) [31].

Later a similar compound was isolated from the bark of African specie of *Croton zambesicus* Muell. by Ngadjui, B. *et al.* [48] and named crotonadiol with $[\alpha]_D$= -28°. Five years later, a compound corresponding to crotonadiol (**42**) was isolated by Yang, B. *et al.* from the bark of *Larix olgensis* Henry var. *koreana* Nakai and its structure was proved by spectral analysis and X-ray diffraction [49].

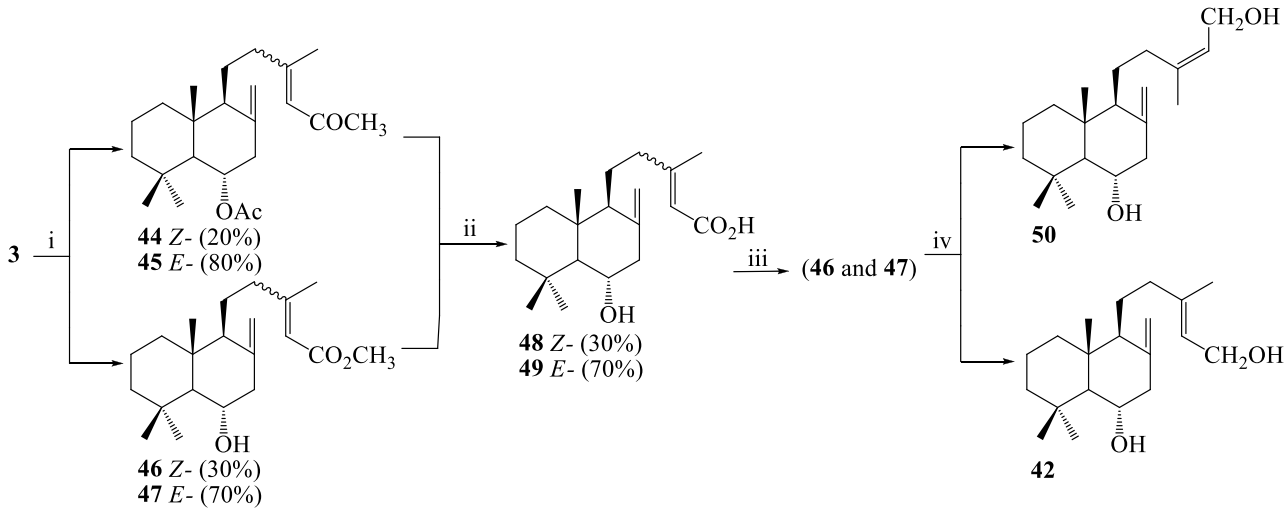
The latest syntheses of (+)-crotonadiol (**42**) were reported by Vlad, P. *et al.* [32]. The first three-step attempt included allylic isomerisation of larixyl acetate (**2**) with PBr_3, substitution of the bromine atom from the molecule of **40** with larixyl diacetate, **41** formation and saponification of the last into (+)-crotonadiol (**42**) (Scheme 7). The second option consisted of acetylation of larixyl acetate (**2**) with AcCl in DMA, allylic isomerization of obtained diacetatete **43** in the presence of $PdCl_2{\cdot}(CH_3CN)_2$, followed by saponification of allylic diacetatete **41** into final (+)-crotonadiol (**42**).

Next, Vlad, P. *et al.* tried to improve the yield of (+)-crotonadiol (**42**) [32]. For this, 6*α*-acetoxy ketone **3** was subjected to Wittig-Horner reaction, which led to a mixture of chromatographic separable products in ~1:3 ratio (Scheme 8). According to NMR analysis, the less polar fraction consisted of a mixture of 13*E*- and 13*Z*-acetoxy esters **44** and **45** (8:2), and the more polar one of 13*E*- and 13*Z*-hydroxy esters **46** and **47** (7:3). This composition means that during the Wittig-Horner reaction partial saponification of 6*α*-acetoxy group occurred, which led to hydroxy esters **46** and **47**.



Reagents and conditions: (i) PBr_3, Et_2O anh., -6°C, 1 h, then r.t., 12 h; (ii) KOAc, DMF, r.t., 12 h, 39%; (iii) KOH, EtOH, reflux, 2 h, 98%; (iv) AcCl, DMA, 5°C, 12 h, 94%; (v) $PdCl_2{\cdot}(CH_3CN)_2$, THF, Ar, r.t., 12 h, 86%.

Scheme 7. Synthesis of (+)-crotonadiol (42) from larixyl acetate (2) [32].



Reagents and conditions: (i) $NaOCH_3$, $(CH_3O)_2P(O)CH_2CO_2CH_3$, C_6H_6, reflux, 2 h; (ii) KOH, EtOH, reflux, 1 h; (iii) $TMSCHN_2$ (2M), THF, MeOH, r.t., 0.5 h; (iv) $LiAlH_4$, Et_2O, Ar, 0°C, 3 h.

Scheme 8. Synthesis of (+)-crotonadiol (42) from 6*α*-acetoxy ketone 3 [32].

The separate saponification of mixtures **44**/**45** and **46**/**47** gave chromatographically separable 13*E*- and 13*Z*-hydroxy acids **48** and **49**, which were methylated and reduced with $LiAlH_4$ into (+)-crotonadiol (**42**) ($[\alpha]_D$= +19.3°) and its (+)-*E*-isomer **50** ($[\alpha]_D$= +41.35°). The spectral data of (+)-crotonadiol (**42**) are in accordance with those reported before, while the (+)-*E*-isomer **50** was reported for the first time.

To note, that by comparing the physicochemical constants of the final compounds **42** and **50**, it can be concluded that compound **51** ($[\alpha]_D$= -28.0°) reported by Ngadjui, B. *et al.* belongs to the *ent*-labdane series of diterpenes [48] (Figure 4).

The (+)-6*β*-isovaleryloxylabda-8,13-diene-7*α*,15-diol (**55**) isolated from the mucus of *Trimusculus reticulatus* exhibited potent repellent activity against starfish [55]. Only one synthesis of this compound was performed from (+)-larixol (**1**) and reported by Morin, C. and co-workers in nine steps and ~30% overall yield [56].

Unfortunately, the last published synthesis based on (+)-larixol (**1**) dates from 2014 [14], the scientific papers that followed, referred to phytochemical analysis of Larch spp. and other conifer species of different geographic origin or their hybrids, and described wood analysis and biological activity assessments of the extracts from mentioned conifer against different pests. Along with other metabolites, the presence of compounds **1** and **2** were reported for the first time in the sources under research. Other scientific data on this topic are discussed in chronological order.

The results of GC-MS analysis of oil extractives components (OECs) from wood and bark *of Pinus sylvestris, Abies alba, Picea abies* and *Larix decidua* growing in Czech Republic were reported by Salem, M. *et al.* [57]. *Epi*-manool (**56**) (6.31%) was detected in *n*-hexane extract from the bark of *Abies alba* and larixyl acetate (**2)** (0.82%) in that from *Picea abies* (Figure 7). The highest content of 13-*epi*-manool (**56**) (2.77% and 15.40%) and (+)-larixol (**1**) (4.85% and 33.29%) was found in the wood and bark extracts of *Larix decidua*.

Using the same method, the chemical composition of the methanolic stem wood and bark extracts of Norway spruce *(Picea abies* (L.) Karst.) and European larch *(Larix decidua* Mill.) were evaluated by Salem, M. *et al.* [58]. Among all the identified components, the major 13-*epi*-manool (**56**) (5.07-12.48%), abietic acid (**57**) (26.8-30.5%), dehydroabietic acid (**58**) (5.9%) and (+)-larixol (**1**) (14.55-15.8%) (Figure 5) were reported.

In an attempt to find effective natural remedies against mildew, caused by the oomycete *Plasmopara viticola,* extracts of the bark of eight important northern forestry species (*Picea abies* L. H. Karst, *Picea jezoensis* (Siebold & Zucc.) Carriere, *Larix decidua* Mill., *Larix sibirica* Ledeb., *Larix gmelinii* (Rupr.) Kuzen., *Populus tremula* L., *Pinus sylvestris* L., *Abies nephrolepis* (Trautv. Ex Maxim) Maxim.) were screened [59].

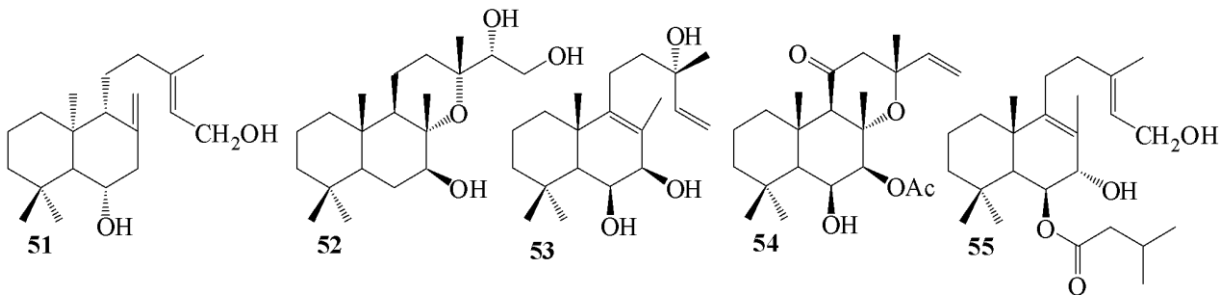


Figure 4. The (-)-*ent*-crotonadiol (51) and labdane diterpene derivatives of (+)-larixol (1) [49-55].

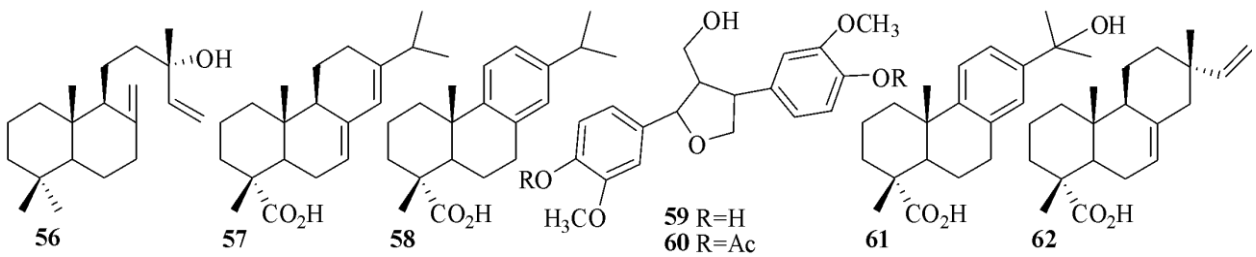


Figure 5. The major components 56-62 of some conifer species [56-61].

From the most active dichloromethane extracts, have been isolated and identified the following compounds: (+)-larixol (**1**), larixyl acetate (**2**), lariciresinol (**59**), lariciresinol acetate (**60**) (from *Larix* spp.) and 15-hydroxidehydroabietic acid (**61**) (from *Pinus sylvestris*) (Figure 5).

The dichloromethane, ethyl acetate and methanol extracts from the bark extracts of Larch *(Larix decidua* Mill.) were tested as alternatives to copper fungicides used against grapevine downy mildew *(Plasmopara viticola)* [60]. According to the GC-MS and GC-FID data, the main constituents of the mentioned extracts were (+)-larixol (**1**) (0.19-0.31%), larixyl acetate (**2**) (0.63-4.37%) and *epi*-manool (**56**) (omitted).

The chemical composition and distribution of the soluble sugars, starches, proteins, terpenoids and phenolic compounds in the rhytidome and secondary phloem of the Kuril larch *(Larix gmelinii* var. *japonica)* and Japanese larch *(Larix kaempferi)* species, and their F_1 hybrid *(Larix gmelinii* var. *japonica x Larix kaempferi)* was studied by Seki, K. *et al.* [61]. The highest content of (+)-larixol (**1**) and larixyl acetate (**2**) was found in the rhytidome of *Larix gmelinii* 4186/1675 µg/g), followed by F_1 hybrid (2719/1545 µg/g) and *Larix kaempferi* (145/445 µg/g). The same order is kept for their content in the secondary phloem of the species *Larix gmelinii* (1646/1196 tig/g), followed by the F_1 hybrid (1262/1069 µg/g) and *Larix kaempferi* (61/199 µg/g).

In order to develop an efficient procedure of larch wood capitalization, the analysis of the wood extractives obtained with an accelerated solvent extractor (ASE) from three different tissues, sapwood, sound knotwood and dead knotwood was performed [62]. Using different methods of analysis (GC-MS, FT-RAMAN, FT-IR and FT-NIR), Wagner, K. *et al.* found that the *n*-hexane extracts from dead knotwood samples yielded more (+)-larixol (**1**) and resin acids, *e.g.* isopimaric acid (**62**) than the other samples (Figure 5).

Most of the recently published bibliographical sources are referring to phytochemical analysis of essential oils and/or extracts obtained from some species of angiosperms, where (+)-larixol (**1**) and larixyl acetate (**2**) which normally are chemomarkers specific for coniferous species have been identified for the first time. As mentioned above, scientific results are discussed chronologically.

The comparative study of essential oils obtained by hydro-distillation of stem and aerial parts of *Origanum majorana* Linn. (*Lamiaceae*) was reported by Prerna, G. *et al.* [63]. A total number of seventy-eight compounds were identified in the stem oil and eighty-seven in the oil from the aerial part of which linalool (**63**) and estragole (**64**) were found as main components (41.31-45.05% and 14.14-25.62%, respectively) and a trace amount of (+)-larixol (**1**) (0.04%) was detected (Figure 6).

The methanolic extract from *Acalypha indica* L. leaves, a species originated from India, has the capacity to act as a radical scavenger and also showed potential cytotoxic activity [64]. Ravi, S. *et al.* have mentioned that this was due to a high content of polyphenols. However, the HR-LC/Q-TOF/MS analysis of *Acalypha indica* extract for the first time confirmed, among the eighty-seven components, there was a low content of larixyl acetate (**2)** (~0.26%) [64].

The presence of (+)-larixol (**1**) (0.2%) was reported by Sharma, V. *et al.* in the essential oil of *Ocimum tenuiflorum*, together with the main constituents *β*-caryophyllene (**65**) (38.90%), eugenol (**66**) (19.63%), caryophyllene oxide **67** (20.39%) and other thirty-six compounds [65] (Figure 6).

The results of GC-MS analysis of the essential oil obtained from three species of the genus *Dracocephalum* L. growing in Kazakhstan were reported by Suleimen, Y. *et al.* [66].

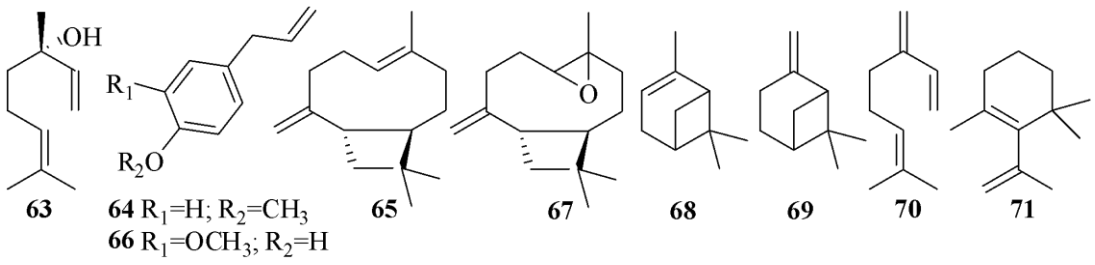


Figure 6. The main constituents of essential oils and extracts from some medicinal species [62-65].

Essential oils were obtained from the aerial parts of plants *Dracocephalum nutans, Dracocephalum ruyschiana, Dracocephalum thymiflorum* in an average yield of ~0.2%. More than over 90 constituents were identified in the volatile oils and the analysis proves that chemical composition of the species under research is quite different. The main constituents were the typical monoterpenes, sesquiterpenes and their oxygenated derivatives, such as *a*-pinene (**68**) and *β*-pinene (**69**), *β*-myrcene (**70**), *β*-cyclocitral (**71**), (*E*,*E*)-nepetalactone (**72**), (*Z*,*E*)-nepetalactone (**73**), *β*-bourbonene (**74**), germacrene D (**75**), palustrol (**76**), spathulenol (**77**), *β*-caryophllene oxide (**67**), humulene oxide (**78**) and others (Figures 6 and 7).

The diterpene fraction of the EOs is represented by (*E*)-phytol (**79**) (0.4% *Dracocephalum nutans;* 0.7% *Dracocephalum ruyschiana),* biformen (**80**) (0.3%) and (+)-larixol (**1**) (0.5%), both present only in the sample obtained from *Dracocephalum nutans* (Figure 8).

The essential oil of *Trembleya parviflora* (D. Don) Cogn., is a rich source of terpenic compounds including diterpenoids. Farias, W. *et al.* monitored the variation of *Trembleya parviflora* essential oil content and its composition during the year and established the maximal concentration of constituents [67]. The monoterpenes as *a*-pinene (**68**) and *β*-pinene (**69**) (25.4 and 19.8% in June and July, respectively) and *α*-terpineol (**81**) (September, 16.5%) were major compounds, while the highest content of diterpenoid (+)-larixol (**1**) was found in March (7.3%).

Another natural source where (+)-larixol (**1**) (0.3%) was identified for the first time, are the aerial parts of *Leonurus pseudomacranthus* Kitag [68]. It was identified during essential oil analysis together with laddane diterpenoids (-)-sclareol (**82**), which is the major component (34.8%), sclareol oxide (**83**) (0.3%) and manoyl oxide (**84**) (0.4%) (Figure 8).

As with other species, the major components of *Leonurus pseudomacranthus* essential oil are sesquiterpenes like *α*-longipinene (**85**) (2.1%), *β*-caryophyllene (**65**) (7.1%) and *α*-muurolene (**86**) (Figure 9). The essential oil showed excellent antimicrobial activity and antioxidant potential.

As stated by Li, X. *et al.*, after fractionation of the methanol extract of *Hypericum longistylum* with petroleum ether, (+)-larixol (**1**) was isolated by column chromatography, together with other compounds, and its structure was proved by instrumental analysis and comparison of spectroscopic data with previously reported [69].

The presence of (+)-larixol (**1**) (0.28%) was reported by Liu, H. *et al.* in the volatile oil obtained from the stem bark of *Taiwania flousiana* Gaussen (Taxodiaceae) [70].

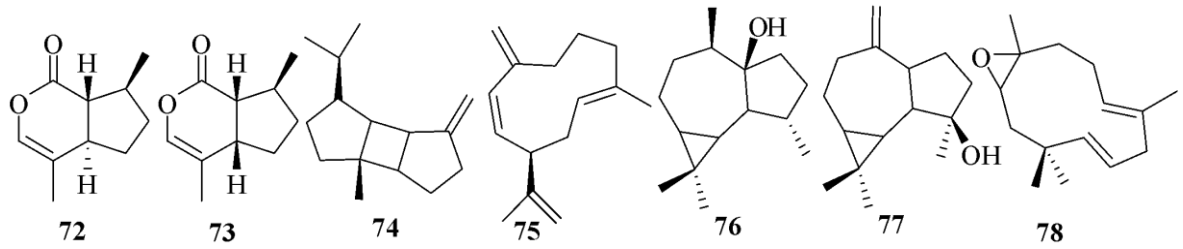


Figure 7. The main terpenic constituents of essential oils of *Dracocephalum* spp. [65].

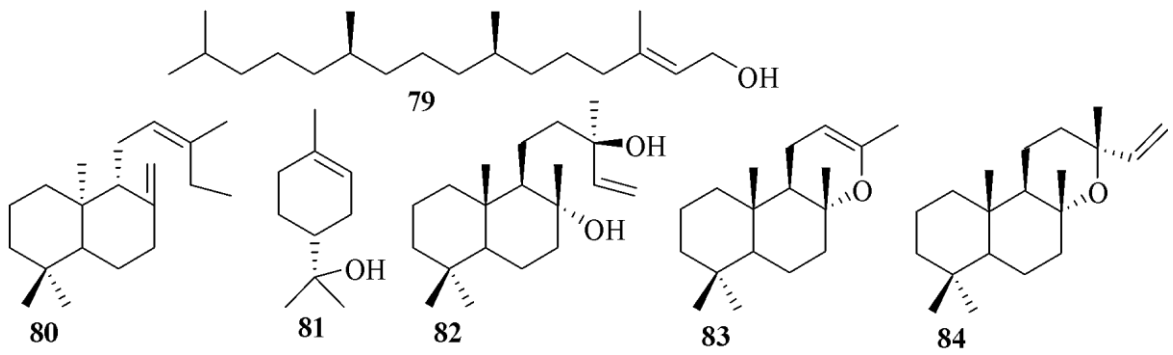


Figure 8. Other constituents of essential oils of *Dracocephalum* spp. and *Leonurus* spp. [65-67].

According to Bezerra, F. *et al.*, the major compound found in supercritical carbon dioxide ($SC\text{-}CO_2$) extracts from *Croton matourensis* Aubl. leaves was (+)-larixol (**1**) (24.88-50.57%), compared to the extracts obtained by conventional extraction with *n*-hexane (2.93%) and hydro-distillation (not detected) [71]. It should be mentioned that oxygenated labdane diterpenes are the main fraction of $SC\text{-}CO_2$ extracts (37.15-85.62%) including also the manoyl oxide (**84**) (10.25-26.72%), phytol (**79**) (1.57-7.47%) and 3*α*-hydroxy-manool (**87**) (0.45-7.09%). In contrast to $SC\text{-}CO_2$ extract, HE and HD extracts contain mostly monoterpenes, sesquiterpenes and their oxygenated derivatives, the main components (Figure 9) being linalool (**63**) (35.26-69.98%), (*E*)-caryophyllene (**65**) (6.53-9.94%), *α*-pinene (**68**) (8.82%) and *α*-phellandrene (**88**) (6.20%).

Recent biological investigations of (+)-larixol and larixyl acetate

This subchapter includes the results of recent biological tests, which have highlighted some new properties of vegetal extracts containing (+)-larixol (**1**) and larixyl acetate (**2**), or of their pure forms.

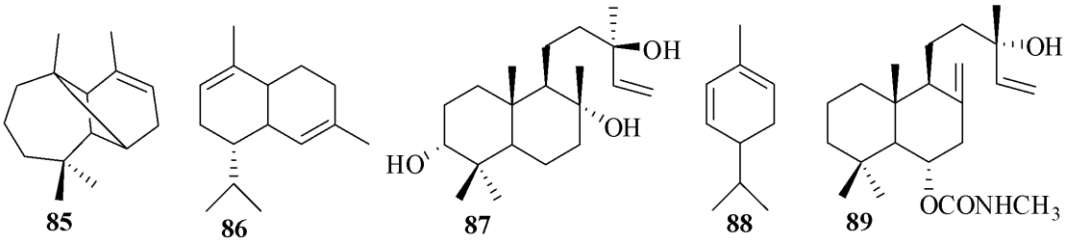
In addition to the chemical composition analysis of methanolic stem wood and bark extracts from *Picea abies* L. Karst. and *Larix decidua* Mill., reported in the previous subchapter, Salem, M. *et al.* also performed the antimicrobial assays [58]. The methanol (95%) extract from *P. abies*/*L. decidua* wood and bark showed good MIC and MFC against *Aspergillus flavus* (0.13 and 0.25 mg/mL), *Candida albicans* (1.74 and 3.52 mg/mL), *Penicillium funiculosum* (0.29 and 0.72 mg/mL) and *Penicillium ochrochloron* (0.19 and 0.42 mg/mL), comparable with Fluconazole and Ketoconazole standards. Unlike other sources, the high activity of the methanolic extract of *L. decidua* bark can be explained by the high summary content ~60% of diterpenoids (2,9-dihydroxyverrucosane, abietic acid and (+)-larixol). The results suggest that the *P. abies* and *L. decidua* extracts have a potential use in food and/or pharmaceutical industries [58].

According to Mulholland, D. *et al.* the most promising anti-mildew (*Plasmopara viticola*) activity was exhibited by the dichloromethane extract from three species of Larch *(Larix decidua* Mill., *Larix sibirica* Ledeb., *Larix gmelinii* (Rupr.) Kuzen.) (at 1 mg/mL, efficacies 88-98%) and Scots pine *(Pinus sylvestris* L.) (at 1 mg/mL, efficacies 50-80%) [59]. The high activity of the extracts against mildew is explained by the presence of the major compounds as lignans (lairciresinol and lariciresinol acetate), and diterpenoids (larixol, larixyl acetate and dihydroxydehydroabietic acid).

In another paper, Thuerig, B. *et al.* mention that the ethanolic extract of Larch bark with a combined concentration of (+)-larixol/larixyl acetate (~66%) showed promising *in vitro* antifungal activity against *P. viticola* at MIC_{100}= 6-23 μg/mL *in planta* semi-controlled conditions at EC_{50}= 0.2-0.4 mg/mL, that means a comparable efficacies of larch extracts reached up to 68% in a stand-alone strategy and 84% in low-copper strategies. This approach can allow the copper reduction in organic vineyards [60].

The methanolic extract of *Acalypha indica* L. leaves, a specie originated from India, has the capacity to act as a scavenger of DPPH radical (at IC_{50}= 28.330 μg/mL), H_2O_2 (at IC_{50}= 84.415 μg/mL), hydroxyl radicals (at IC_{50}= 35.933-84.775 μg/mL) and week metal ions reducer. Also, it showed potential cytotoxic activity (LC_{50}= 140.02 μg/mL) against brine shrimp. Ravi, S. *et al.* mention that all these activities of MEAIL are due to the high content of polyphenolics, flavonoids and saponins [64].

As mentioned above, the essential oil of *Origanum majorana* is one of the new sources where (+)-larixol (**1**) was detected. According to Sharma, V. *et al.*, this EO revealed excellent inhibition activity against the test fungal organisms, with presence of maximum inhibition zone (MIZ= 37 mm) against *Trichophyton mentagrophytes*, (MIZ= 31.67 mm) against *Microsporum gypsium* and (MIZ= 28.33 mm) against *Microsporum nannum*, which is mainly due to mono- and sesquiterpene constituents [65].



85 **86** **87** **88** **89**

Figure 9. Metabolites of *Leonurus pseudomacranthus* essential oil and *Croton matourensis* supercritical carbon dioxide extract [67-72].

As in other cases, the OECs from *Dracocephalum* spp. growing in Kazakhstan are new sources where, among others constituents, (+)-larixol (**1**) was detected, as well. Samples obtained from all three species exhibited acute lethal toxicity towards the larvae of the *Artemia salina* aquatic crustaceans at all tested concentrations (1-10 mg/mL) and low antiradical activity (at 3.51-8.70 %) compared with the standard drug – butylhydroxyanisole at ~80%. Likewise, in this case, Suleimen, Y. *et al.* mention that the activity is due mono-(C_{10}) and sesqui-(C_{15}) terpenic fraction [66].

Fifteen compounds isolated by Li, X. *et al.* from *Hypericum longistylum* were subjected to the separate MMT assay on fibroblast cytotoxicity. According to the test results (+)-larixol (**1**) had no deleterious effects on normal mouse lung fibroblasts and no significant inhibition of vitality [69].

The assessments of biological activities of the essential oil from *Taiwania flousiana* Gaussen. performed by Liu, H. *et al.* showed a wide range of strong algicidal, antifungal, antibacterial and promising antioxidant activities [70].

Surprisingly, *Croton matourensis* has proven to be a new source of (+)-larixol (**1**). Bezerra, F. *et al.* performed biological activity tests of hydrodistillation, hexane and SC-CO_2 extracts from leaves and proved that all of them have exhibited antioxidant activity at 14 mg/mL (IC_{50}= 1531.34, 2680.11, 614.73 g extract/g DPPH). It was mentioned that the SC-CO_2 extract showed potential anti-inflammatory and neuroprotective effects on experimental cerebral ischemia in rats. All these activities of extracts from *Croton matourensis* leaves can be related to the presence of oxygenated diterpenes (37.15-85.62%), especially to (+)-larixol (**1**) and manoyl oxide (**84**) [71].

In the last decades, many efforts have been put in identifying chemical entities that may control TRPC6 activity, a nonselective and Ca^{2+}-permeable cation channel, which mediates pathophysiological responses within pulmonary and renal diseases. Within several preparations of plant extracts, a strong TRPC6-inhibitory activity was found in Larch balsam. By testing, its main constituents (+)-larixol (**1**) and larixyl acetate (**2**) were identified as blockers of Ca^{2+} entry and ionic currents through diacylglycerol- or receptor-activated recombinant TRPC6 channels exhibiting approximately 12- and 5-fold selectivity compared with its closest relatives TRPC3 and TRPC7, respectively. The potent inhibition of recombinant TRPC6 by larixyl acetate (IC_{50}= 0.1–0.6 μM) was confirmed for native TRPC6-like $[Ca^{2+}]_i$ signals in diacylglycerol-stimulated rat pulmonary artery smooth muscle cells [72].

Urban, N. *et al.* synthesized new TRPC6-inhibiting modulators from (+)-larixol (**1**), and tested the potency and selectivity in cell lines stably expressing various TRP channel isoforms [73]. The most promising compound was larixyl *N*-methylcarbamate (**89**) which displayed a favourable potency with an IC_{50} to inhibit wild-type TRPC6 of 0.48 μM that is an about 30-fold higher versus TRPC3 and 5-fold higher versus TRPC7, respectively.

It was proved that (+)-larixol (**1**) and its acetylated congeners possess selective inhibition of the second-messenger-gated cation channel transient receptor potential canonical 6 (TRPC6) over its close isoforms TRPC3 and TRPC7. Haefner, S. *et al.* expanded these findings by chemical diversification of (+)-larixol (**1**) at position C-6, C-9 side chain, C-8 exomethylene group and mixed. As a result of series of screening assays, Haefner, S. *et al.* reported the larixyl *N*-methylcarbamate **89** as an efficient TRPC6 blocker with an IC_{50} value of 5.8 nM that holds promise for the translational treatment of lung ischemia-reperfusion edema (LIRE) [74].

Chen, X. *et al.* reported improving of endothelial function in wild type control mice subjected to mTBI after 7-days of *in vivo* treatment with larixyl acetate (**2**), an inhibitor of TRPC6 channels with an apparent IC50 value of about 0.65 μM, which is 10–100 times lower than that for other members of the TRPC channel subfamily [75].

(+)-Larixol, larixyl acetate and intellectual property protection

As a logical continuation of the research conducted, a number of results found their application in practice and were patented by some of the above cited authors. In continuation, several of the recently published patents will be discussed.

A group of inventors, Meyer, I. *et al.*, was granted with patents [76,77] for an invention which relates to a cosmetic composition and comprises (+)-larixol (**1**) and optionally some components like a tyrosinase inhibitor, a sun protection factor; an antioxidant, an anti-inflammatory agent and a desquamating agent.

Mulholland, D. *et al.* [78] obtained the title of protection on use of extracts from *Larix* spp. (*Larix decidua*, *Larix gmelinii*, *Larix kaempferi*, *Larix sukaczewii* and *Larix sibirica*) for treating,

preventing or reducing an oomycete pathogen infection. They mention that these properties are due to components such as (+)-larixol (**1**) or lariciresinol (**59**) or an active derivative thereof, such as larixyl acetate (**2**) or lariciresinol acetate (**60**). They mention, that in particular dichloromethane or methanol extracts may treat or prevent an infection caused by *Plasmopara* spp. or *Phytophthora* spp., in particular *Plasmopara viticola* or *Phytophthora* infestans. An infection to treat can be selected from downy mildew, late blight of potato, sudden oak death, rhodendron root rot, ink diseases of European chestnut, pythium damping off or white blister rust infection.

Next inventions belong to microbiology, more exactly to microbial transformations and microbial production of terpenes [79,80]. Schrader, J. *et al.* claimed a process for *de novo* microbial synthesis of sesquiterpenes or diterpenes, including (+)-larixol (**1**), using genetically modified methylotrophic bacteria (*Myxococcus xanthus*, *Methylobacterium extorquens*) and alternative carbon sources like methanol and/or ethanol.

The list of recently published patents concludes with a patent for a method of extraction, purification, testing and application of *Leonurus pseudomacranthus* essential oil claimed by Lai, P. *et al.* [81]. It comprises the condition for the essential oil extraction, the procedures of its purification and GC-MS analysis. According to Lai, P. *et al.*, the *Leonurus pseudomacranthus* essential oil can be used as a bacteriostatic agent against strains of *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*.

Conclusions

This review presents scientific data regarding the syntheses made based on (+)-larixol and larixyl acetate, published since 2000. Currently, one of the major concerns of researchers in the field are phytochemical studies, resulting in the identification of, new natural sources that contain compounds from the title.

Another current concern of researchers, which has provided excellent practical results, is the *in vitro* or *in vivo* testing of (+)-larixol and larixyl acetate or their derivatives, or plant extracts, especially those obtained from some species of conifers.

Based on the above, it can be concluded that in recent decades in the field of (+)-larixol chemistry, the balance has shifted from fundamental studies in the direction of practical applications. However, it can be stated with all certainty that (+)-larixol, larixyl acetate, their derivatives and the products that contain them are still an interesting object for research.

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