SDRP Journal Of Plant Science

Sift Desk Research Page

Open Access

Review Article

Natural hydroperoxides as potential terapeutical agents

Valery M. Dembitsky*
Institute of Drug Discovery, P.O. Box 45289, Jerusalem 91451, Israel
***Address:** 8 Ha-MarpeStr., P.O. Box 45289, Jerusalem 91451, Israel
Tel/fax: +972 526 877444.

Received date: 11-08-2015; **Accepted date:** 19-09-2015; **Published date:** 21-09-2015
Keywords: Hydroperoxides, acyclic peroxides, plants, algae, fungi, activities

Abstract
Peroxy-containing metabolitesare an interesting group amongbiological active natural compounds. These metabolites contain a peroxide group (-O-O-) in which each oxygen atom is bonded to the other oxygen an to another atom. β-Oxygen in hydroperoxide group is considered as moreactive.Present review describes research on more than 100 natural hydroperoxidesand rare acyclic peroxides isolated from plants, algae, and fungi. Intensive searches for new classes of biologicallyactive metabolites produced by terrestrial and marine origin have resulted in the discovery of dozens of compounds possessing high antimalarial,antibacterial, cytotoxic, and other pharmacological activitiesas an important source of leads for drug discovery.

Introduction

More than 1,000 peroxides (hydro-, acyclic and endo-) have been isolated and structurally characterized from natural sources, mainly as constituents of fungi, fungal endophytes, and plants; they also were found in freshwater and marine algae, invertebrates, and other organisms[1-5].

Among naturally occurring hydro- and endoperoxides represented a large group compounds which are shown to possess antimalarial, antibacterial, cytotoxic, and many other activities. In the past several decades, natural peroxides have been isolated from a wide variety of fungi, plants, and marine organisms. Extensive pharmacological screening performed on aquatic and/or terrestrial species resulted in discovery of novel anti-tumor, antibacterial, and mainly antimalarial agents[6-9]. The purpose of this review is to summarize bioactive metabolites of more than 100 natural hydroperoxides, belonging to diverse structural classes: terpenes, steroids, alkaloids, fatty acids, and other compounds.

This paper reviewed more than one hundred of new and active peroxy natural metabolites produced by plants, algae, fungi, and described their structures, chemistry, and pharmacological activities.

Fungal hydroperoxides

Unusual spiro[4.5]decane sesquiterpenes, cordycepol A, B and C (1), were isolated from the cultured myceliaof parasitic fungi-Cordyceps ophioglossoides (family Ophiocordycipitaceae). Isolated compounds showed the cytotoxic activities (IC50 values in the range of 12-33 μg/mL) against HeLa and HepG2 [10].

Eudesmene-type sesquiterpenes, kandenols C (2) and D (3), have been isolated from Streptomyces sp. HKI0595 derived from the mangrove plantKandelia candelas weak to moderate inhibitors of B. subtilis and Mycobacterium vaccae growth [11].

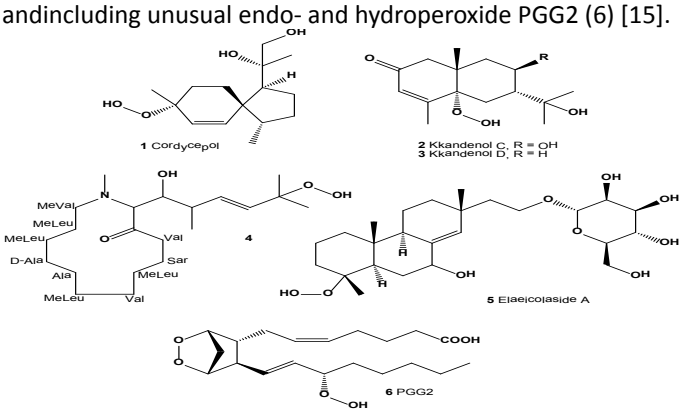
Entomopathogenic species belonging to the genus Tolypocladium, T. terricola, are known as producers of secondary metabolites and possession of relatively strong mosquitocidal activity [12].

Cyclosporins are produced by certain species of the filamentous fungi, belonging to the genus Tolypocladium[2].

Some cyclic peptides and depsipeptides are synthesized in microorganisms by large multienzymes called nonribosomal peptide synthetases. Proven cytotoxic, anti-inflammatory, anticancer, and immunosuppressive activities of some cyclic peptides indicate that these molecules may contribute to the synergistic array of fungal virulence factors and support microbial invasion during fungal infection. Cyclosporin D hydroperoxide (4), was isolated from this cultivated fungus Tolypocladium terricola[13].

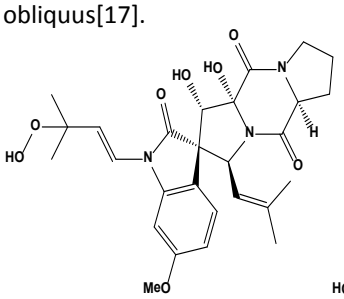
Several isopimarane-type diterpene glycosides, along with an eremophilane-type sesquiterpene, i.e., elaeicolasides A (5), B and C were isolated from the AcOEt extract of the fermented broth of the ascomycete Stilbohypoxylon elaeicola YMJ173. All these compounds inhibited NO production, detected as nitrite in the culture medium, in activated macrophages without any cytotoxicity at a concentration of 100 μM [14].

The opportunistic fungal pathogen Cryptococcus neoformanswas used for production of several species of prostaglandins (PGE2, PGH2 and 15-keto-PGE2) from arachidonic acid, andincluding unusual endo- and hydroperoxide PGG2 (6) [15].

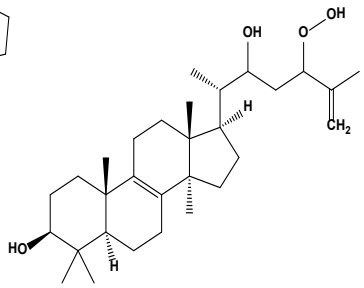


Prenylated indole diketopiperazine alkaloids, spirotryprostatin E (7) has been obtained from the fermentation of Aspergillus fumigatus from a holothurian, Stichopus japonicus (Lingshan Island, Qingdao, China) [16].

Sterols are one of the active classes of compounds in Inonotus obliquus (known as chaga mushroom) for their effective therapy of many diseases. The results indicated that field-grown mycelia contained lanosterol and inotodiol (45.47% and 25.36% of the total sterols, respectively) and other 10 sterols (comprising the remaining 30.17%) including ergosterol biosynthetic intermediates such as 24-methylene dihydrolanosterol, 4,4-dimethylfecosterol, 4-Me fecosterol, fecosterol and episterol. Column chromatography also led to the isolation of lanosterol, inotodiol, trametenolic acid, fuscoporianol B and a triterpenoid fuscoporianol D (8) in field-grown mycelia of Inonotus obliquus[17].



7 Spirotryprostatin E



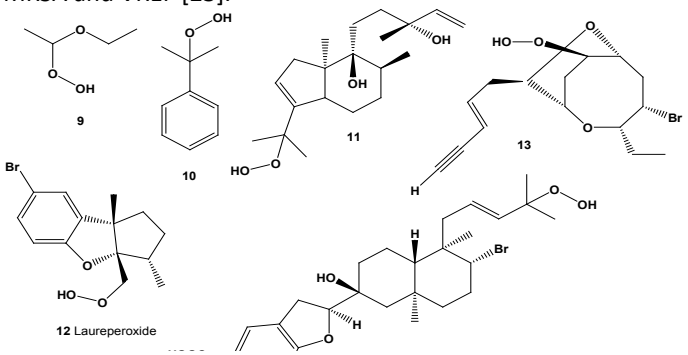
8 Fuscoporianol D

Hydroperoxides from algal species

The (1-ethoxyethy1)hydroperoxide (9) was recovered from several algal species: two brown algae Cladosiphon okamuranus, Analipus japonicus, and red alga Gracilariopsis chorda (Gracilariaceae, Rhodophyta) [18]. Cumene hydroperoxide (10) was detected in green alga Chlorella pyrenoidosa[19].

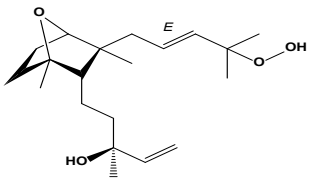
The diterpenoid neoconcinndiol hydroperoxide (11) wasfound as a constituent of red algaLaurencia snyderiae. The suggestion was made that (12) arises fromthe brominated natural product concinndiol, also from L.snyderiae, by solvolytic ring contraction and oxygenation toyield the rearranged allylic hydroperoxide [20].Laureperoxide (13), cuparene-derivedsesquiterpeneisolatedfrom the red alga Laurenciaokamurai (Nanji-Island, China) [21]. Halogenated nonterpenoid C15-acetogenin, laurendecumenyne A(13) has been reported fromthe marine red alga Laurencia decumbens. Cytotoxicity against adenocarcinomic human alveolar basal epithelial cells A549 cells was showed [22].

Bioassay-guided fractionation of extracts from a Fijian red alga in the genus Callophycussp. resulted in the isolation of five new compounds of the diterpene-benzoate class. Isolated bromophycoic acids A, B, C (14), D and E display a range of activities against human tumor cell lines, malarial parasites, and bacterial pathogens including low micromolar suppression of MRSA and VREF [23].

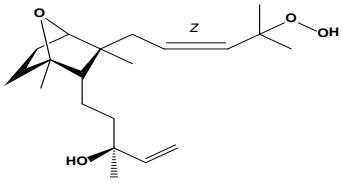


12 Laureperoxide

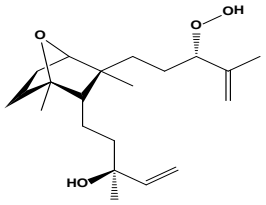
Hydroperoxides have been found in the Russian population of brown alga, Dictyota dichotoma(Troitsa Bay, Sea of Japan, Russia),for example, dictyohydroperoxides A (E-15), A (Z-16), B (17) and C (18) [24].Some isolated compounds showed moderate cytotoxicity against human cancer cell lines. Also, unstable hydroperoxide, dactylohydroperoxide C (18) produced by red algae Laurencia sp. from Tenefire (Canary Island) [25].



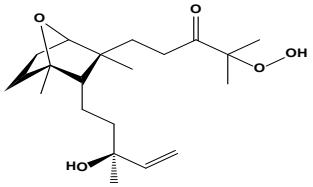
15 *E*-Dactylohydroperoxide A



16 *Z*-Dactylohydroperoxide A



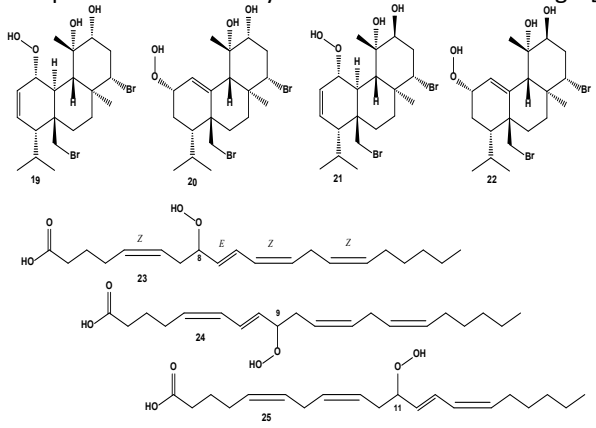
17 *E*-Dactylohydroperoxide B



18 *E*-Dactylohydroperoxide C

Two bioactive brominated diterpenes, cytotoxic bromoditerpene (19) and antibacterial bromoditerpene 2S-hydroperoxy-12R-hydroxy-isobromosphaerol (20)have been isolated from the marine red alga Sphaerococcus coronopifolius (also known as Hematocelis fissurata). The structure of the previously reported 12S-hydroxy-bromosphaerodiol (21) and 2S,12S-dihydroxyisobromo-sphaerol (22) were revised [26 and 27, respectively].

Several hydroperoxidesas derivatives of the arachidonic metabolites with the lipoxygenase in marine algae have been detected. It was reported that eicosanoids, 12(S)- and 15(S)-hydroperoxyeicosatetraenoic acid were the intermediate product of major aldehyde flavor formation [3(Z)- and 2(E)-nonenal and n-hexanal] in an edible brown alga, Laminaria angustata via lipoxygenase (LOX) and hydroperoxide lyase pathway. Three eicosanoides have been found after enzymic formation and identified as 8-, 9-, and 11-hydroperoxy-eicosa-tetraenoic acids (23-25, respectively) by HPLC. These represented the mechanism of positional selectivity of LOX in this marine alga [28].

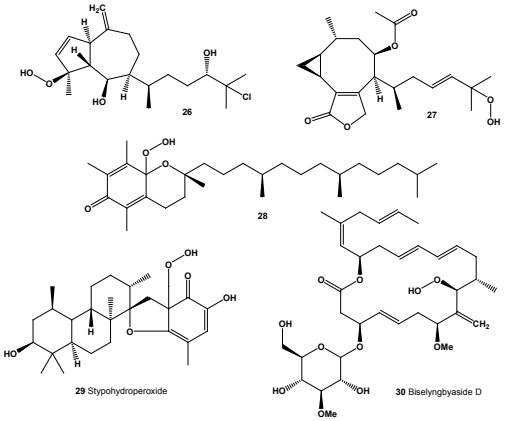


When long-chain saturated and unsaturated fatty acids were incubated with crude enzyme of marine green alga Ulva pertusa (sea lettuce), the corresponding (R)-2-hydroper-

oxy acids: 2-hydroperoxy-hexadecanoic,2-hydroperoxy-9(Z)-octadecenoic, 2-hydroperoxy-9(Z),12(Z)-octadecadienoic acids, respectively) were found to have high enantiomeric excess (>99%). In a similar administration except, the (R)-2-hydroperoxy-acid was obtained from the incubation of palmitic acid with crude enzymes of a variety of marine algae. Thus, authors found that not only green algae but also brown and red algae are capable of enantio-selective 2-hydroperoxylation of palmitic acid [29].Two bioactive compounds, dictyohydroperoxide (26) and hydroperoxy-acetoxycrenulide (27), containing hydroperoxyl groups rarely found in algal terpenoids were isolated from the Russian population of brown alga Dictyota dichotoma. Isolated compounds showed moderate cytotoxicity against human cancer cell lines [24].8a-hydroperoxy-α-tocopherone (28), the primary oxidation product of α-tocopherol by singlet oxygen, it was isolated from Chlamydomonas reinhardtii cultures during high light stress under variety of conditions (presence of inhibitors, an uncoupler, heavy water) [30].

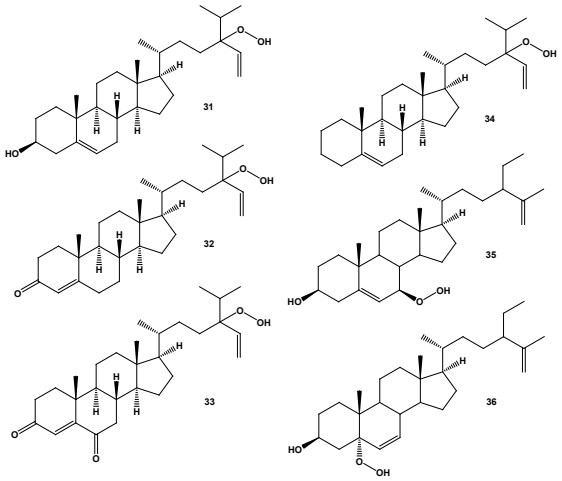
Several biological active meroditerpenoids stypohydroperoxide (29), 2β,3α-epitaondiol, flabellinol, flabellinone, stypotriolaldehyde, along with known compounds from the marine brown alga Stypopodium flabelliforme collected in Papua New Guinea. All of the new metabolites were moderately toxic to murine neuro-2a cells (LC50 2-25 μM), and 2β,3α-epitaondiol, flabellinol, and flabellinonepossessed potent sodium channel blocking activity [31].

Marine cyanobacterium Lyngbya sp. led to the isolation of biselyngbyasides A, B, endo-peroxide biselyngbyasideC, and hydrobiselyngbyasideD (30), collected on Tokunoshima Island (Japan) [32,33]. Isolated biselyngbyasides showed growth-inhibitory activity and apoptosis-inducing activity against both HeLa S3 cells and HL60 cells. The fura-2 method revealed that biselyngbyasides increased the cytosolic Ca2+ concentration in HeLa S3 cells [33].



Cytotoxic steroids (31, 32 and 33) have been recovered from the brown alga Turbinaria conoides. The cytotoxicity in HeLa cells was expressed in terms of 50% cytotoxic concentration (CC50). These oxygenated steroids exhibited cytotoxicity against HeLa cells with CC50 values ranging from 60.9 μg/mL to >100 μg/mL [34]. Sterol, 24(R)-hydroxy-24-vinylcholesterol (31) has been isolated from Sargassum oligocystum (Heterokontophyta), which it is one of the most abundant algae distributed in the Persian Gulf [35], and in Sargassum fusiforme[36]. This compound (31) was also found in red alga Ceratodictyon spongiosum (Rhodymeniaceae)[37].

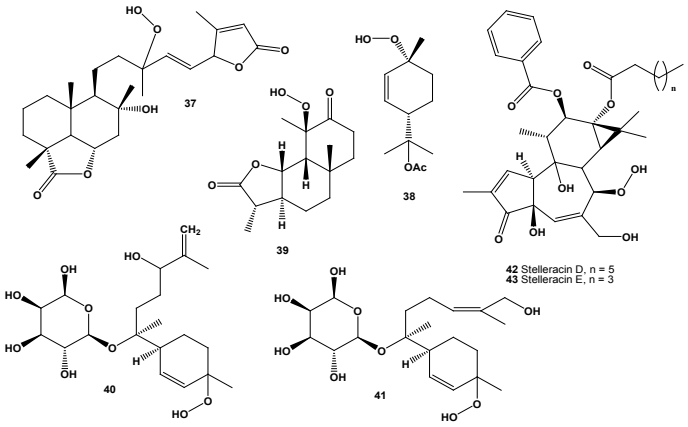
Several unusual glycerolipids, including at 24-ethylcholest-4,24(28)-dien-3β-ol,24-vinylcholest-5-en-24ζ-hydroperoxy (34) were isolated frommarine brown algaSargassum parvivesiculosum [38].Genus Codium contains a lot of different lipophylic metabolites [39], and sterols [40]. The two hydroperoxy clerosterols (35 and 36) were isolated from the the Indo-Pacific marine green alga Codium arabicum [41]. The compounds displayed significant cytotoxicity toward various cancer cell lines.



Hydroperoxides from plant species

Bioactive metabolite (37) was isolated from the aerial parts of Salvia sahendica (family Lamiacea; it is known that Salvia genus showed antibacterial effects on Klebsiella pneumonia, Staphylococcus aureus and Pseudomonas aeruginosa), together with several known compounds, comprising a sesterterpene, a sesquiterpene, a diterpene, triterpenes,steroidal compounds, and flavonoids [42]. A p-menthane hydroperoxide, (1R,4S)-1-hydroperoxy-p-menth-2-en-8-ol acetate (38), astrypanocidal agent against epimastigotes of Trypanosoma cruzi,was isolated from dried leaves ofan aromatic evergreen tree Laurus nobilis (family Lauraceae) [43]. Plant metabolite (39) exhibited antitrypanosomal activityagainst Trypanosoma brucei[44].

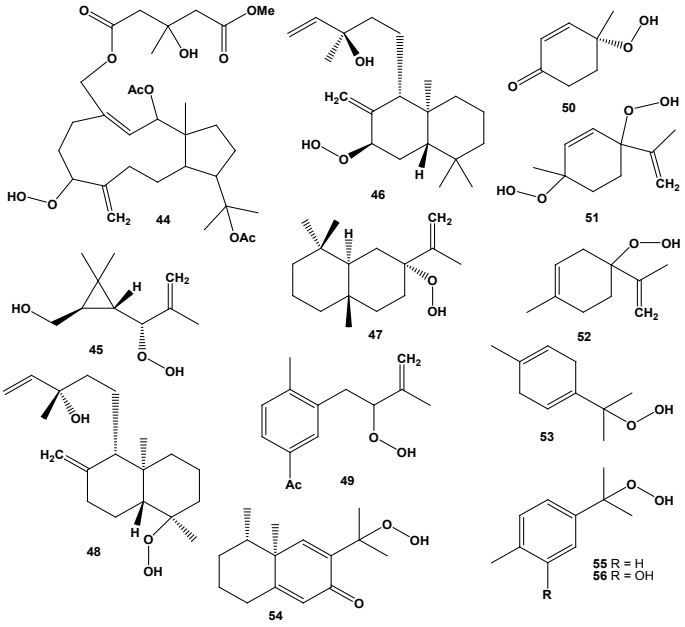
The aerial parts of the Mediterranean weed Carthamus glaucus (family Compositae) afforded an unusual triglyceride (E-2-crotonyl-sn-1,3-distearolylglycerol), and a series of bisabolane fucopyranosides variously acylated on the sugar moiety, and its peroxy derivatives, such as (40) and (41). Isolated fucopyranosidesare aspotential an anti-inflammatory cosmetic ingredient in current short supply in its natural form. A comparative investigation of the activity of isolated metabolites involved in inflammation and cancer pathways (NF-κB and STAT-3) showed only marginal activity on NF-κB inhibition for all compounds [45].Interesting tigliane-type diterpenes, stelleracins A, B, C, D (42) and E (43), were isolated from the roots ofa perennial herbaceous plant Stellera chamaejasme(Thymelaeaceae), from the Qinghai-Tibet Plateau and in adjacent regions. The isolated compounds showed potent anti-HIV activity (EC90 0.00056-0.0068 μM) and relatively low or no cytotoxicity (IC50 4.4-17.2 μM). These compounds represent promising new leads for development into anti-AIDS clinical trial candidates [46].



A dolabellane diterpene derivative with the naturally rare peroxy function was identified as Me ester of 2,18-O-diacetyl-16-O-(3-hydroxy-3-methylglutaryl)-7-hydroperoxy-dolabella-3,8(17)diene-2,16,18-triol (42) was isolated from the aerial parts ofthe herb Cleome droserifolia (syn. Roridula droserifoli) [47]. A trans-chrysanthemic monoterpenoid hydroperoxide (43) has been isolated from the aerial parts of Santolina insularis, a bush endemic to Sardinia. S. insularis is a medicinal plant whose essential oil showed antiviral and anti-bacterial activities and potent and selective cytotoxic activity against the human colon carcinoma cell line. The occurrence of several chemotypes makes the taxonomic identification of S. insularis hard to achieve [48]. The biological activity of S. insularis was also demonstrated against Staphylococcus aureus, Escherichia coli, Candida albicans, Candida tropicalis and Cryptococcus neoformans [49].

Three sesquiterpene hydroperoxides (44-46), together with known compounds, germacrone, ent-germacra-4(15),5,10(14)-trien-1α-ol and teucdiol A were isolated from the aerial parts of Aster spathulifolius (family Compositae). The isolated compounds were tested for their cytotoxicity against five human tumor cell lines in vitro using a SRB method. The two hydroperoxides (44) and (45), showed moderate cytotoxicity against human cancer cells with ED50 values ranging from 0.24 to 13.27 μg/mL [50].

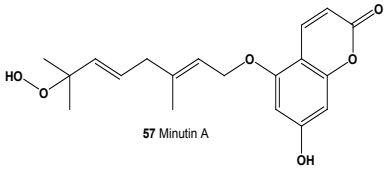
Hydroperoxy terpene (47) was isolated from Juniperus przewalskii(family Cupressaceae; a dominant tree species endemic to the northeast Qinghai-Tibetan Plateau), together with several known terpenes, including, 3α-hinokiol and 3α-hydroxymannol which exhibited effective anti-tumor activities to cervical carcinoma (HeLa) and human ovarian carcinoma (HO-8910) cell lines [51].The lipophilic extract of the fresh water liverwort Riella helicophylla yielded several monoterpenes and diterpenes [52]. Several monoterpenes were hydroperoxides (48-53, 55 and 56) [53]. The 11-hydroperoxy-6,9-eremophiladien-8-one (54), along with oleanolic acid, β-amyrin, β-amyrin acetate and (+)-lupeol, were isolated from the EtOH extracts of Ligularia kanaitzensis (family Compositae) [54].

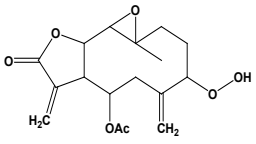


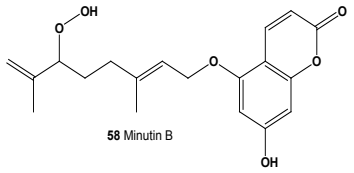
Monoterpene coumarins, minutin A(57) and B (58) were purified fromthe citrus plant Micromelum minutum(family Rutaceae) leaves. Isolated compounds had some inhibitory activity against one or more lung adenocarcinoma (SBC3 and A549) and leukemia (K562 and K562/ADM) cell lines in vitro. Minutin B (57) had the strongest cytotoxic activity against SBC3, A549, K562, and K562/ADM cell lines, with respectively 9.6, 17.5, 8.7, and 6.7 μM [55]. Schinchinenins E and F (59 and 60) are highly oxygenated triterpenoids that contain a hydroperoxyl moiety, which is rare in compound from the Schisandra genus. Some compounds showed activities against HSV-2 and adenovirus [56].

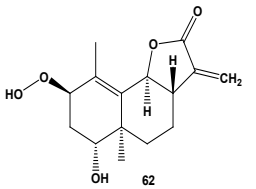
The active constituents of bark and leavesof the traditionally used antimalarial plantLiriodendron tulipifera(known as the tulip tree, American tulip tree) by antiplasmodial-assay guided fractionation. Leaves yielded two known sesquiterpene lactones, peroxyferolide (61) and lipiferolide with antiplasmodial activity. The antiplasmodial activity of compound (61) (IC50 = 6.2 μg/mL) was reported. This work supports the historical use of Liriodendron tulipifera as an antimalarial remedy of the United States and characterizes its antiplasmodial constituents [57].

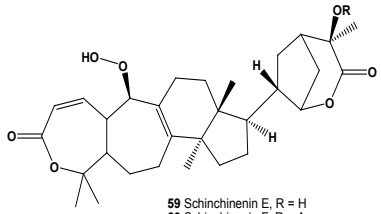
Several sesquiterpenes, together with compounds (62) and (63) were isolated from leaves ofan aromatic evergreen tree Laurus nobilis (also known as Bay leaf).Most of these compounds exhibited moderatetosignificant cytotoxicity toward K562 leukemia cells [58].Lindenane sesquiterpenes, spicachlorantins A (64) and C (65) were isolated from the wholedicotyledonousplant of Chloranthus serratus(family Chloranthaceae). These isolates were evaluated for their inhibitory effects on lipopolysaccharide-induced nitric oxide production in RAW264.7 cells. Spicachlorantin A and two known compounds, shizukaols B and D, showed significant anti-inflammatory activities, with IC50 values of 0.22, 0.15, and 7.22 μM, respectively [59].

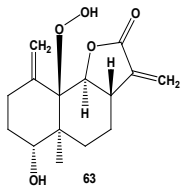






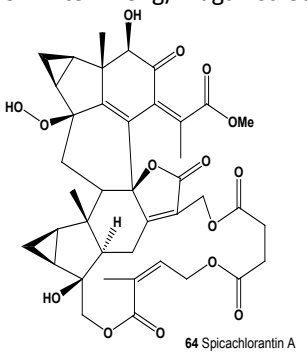


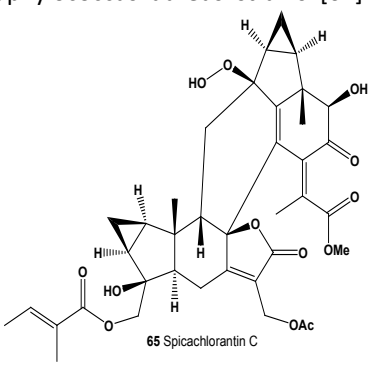


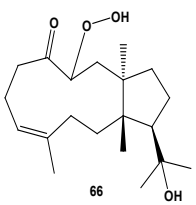


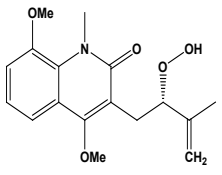
Several bioactive compounds, including (1R,3S,7E,11S,12R)-3-hydroperoxy-dolabella-4(16),7-dien-18-ol (66), was found in leaves extract of he oriental medicinal plantAglaia odorata (family Meliaceae, known as Chinese perfume plant). All isolated compounds possessed potent nitric oxide inhibitory activity with IC50 values ranging from 2.1 to 14.2 μM, these being better than that of the positive control, indomethacin (IC50 = 14.5 μM) [60].

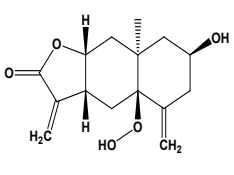
A new hydroperoxyquinolone alkaloid, glycopentaphyllone (67) was isolated from the fruits of lowering plant-Glycosmis pentaphylla (family Rutaceae), known commonly as orangeberry and gin berry. Compound showed antibacterial activity against Escherichia coli TISTR 780, Salmonella typhimurium TISTR 292, Staphylococcus aureus TISTR 1466, and Methicillin-resistant S. aureus SK1 [61].Antibacterial acylphloroglucinols, named olympicins A, B, C, D (68), and (E) were isolated and characterized from the aerial parts of theflowering plantHypericum olympicum cf. uniflorum(family Hypericaceae).Isolated compounds exhibited min inhibitory concentrations (MICs) of 1 to 120□g/L against Staphylococcus aureus strains [62].





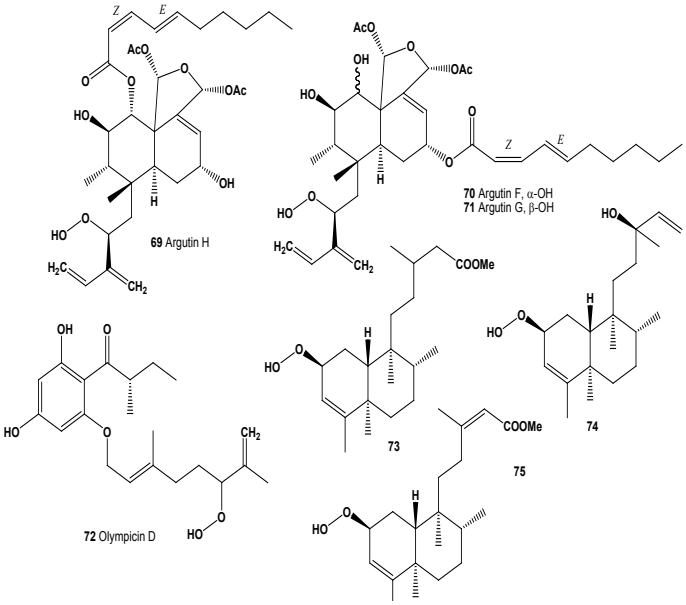




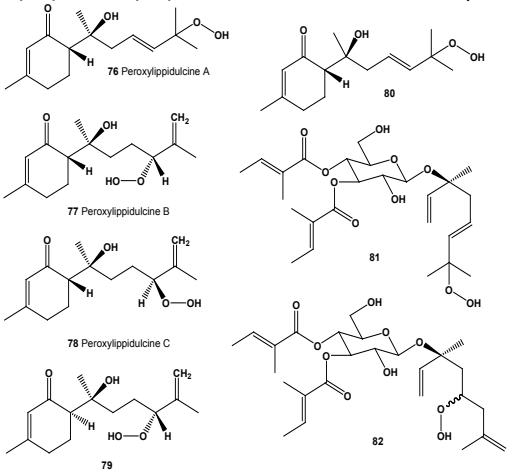


Argutins A, B, C, D, E, F (69), G (70), and H (71) highly oxygenated clerodane diterpenes, were isolated from the plant-Casearia arguta(family Salicaceae) collected in Guatemala. Each of the argutins showed varying levels of synergy with tumor necrosis factor-α-related apoptosis-inducing ligandsensitizers [63].Antibacterial acylphloroglucinols, named olympicins A, B, C, D (72), and (E) were isolated and characterized from the aerial parts of the plantHypericum olympicum cf. uniflorum. All compounds exhibited min inhibitory concentrations (MICs) of 0.5 to 128□g/L against Staphylococcus aureus strains [62].

The genus Aristolochia (known as birthwort, pipevine or Dutchman's pipe)is an important source of physiologically active compounds that belong to different chemical classes, and it is the subject of research in numerous pharmacological and chemical studies [64]. Thus, clerodane diterpenoids isolated from Aristolochia species, compounds (73 and 74, Fig. 20) were isolated from A. esperanzae [65], and compound (75) was identified from A. chamissonis [66].



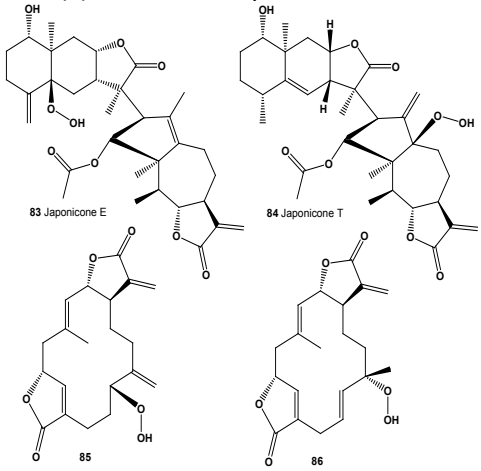
Six new bisabolane-type sesquiterpenes, peroxylippidulcines A-C (76-78), peroxyepilippidulcine B, and others (79,80), have been isolated from the aerial parts of Lippia dulcis (perennial herb; native to southern Mexico), along with two known bisabolane-typesesquiterpenes, seven known flavonoids, and a known triterpenoid [67]. The aerial part of Aster scaber (known as edible Korean chamchwi; family Compositae) yielded two new monoterpeneperoxide glycosides, (81) and (82), and other known compounds[68].



Several dimeric sesquiterpene lactones (japonicones E-L), including a novel sesquiterpene dimer bearing a rare hydroperoxide group (japonicone E, 83), were isolated from the aerial part offlowering plant Inula japonica(family Asteraceae).Compound (83) displayed strong inhibitory activity against LPS-induced NO production in RAW264.7 macrophages [26]. From the same species afforded additional related dimeric sesquiterpene, japonicone T (84) [27].Cembrane-type diterpenoids with a trans-fused □-methylene-□-lactone, including two cembrane hydroperoxides 4-methylene-5β-hydroperoxy-ovatodiolide (85) and 4α-hydroperoxy-5-enovatodiolide(86) were isolated from a methanol extract ofIndian Catmint Anisomeles indica(syn:Nepeta indica, Anisomeles ovata). Compound (86) exhibited cytotoxicity against a small panel of human cancer cell lines, and showed inhibitory effects on antiplatelet aggregation induced by thrombin [69].

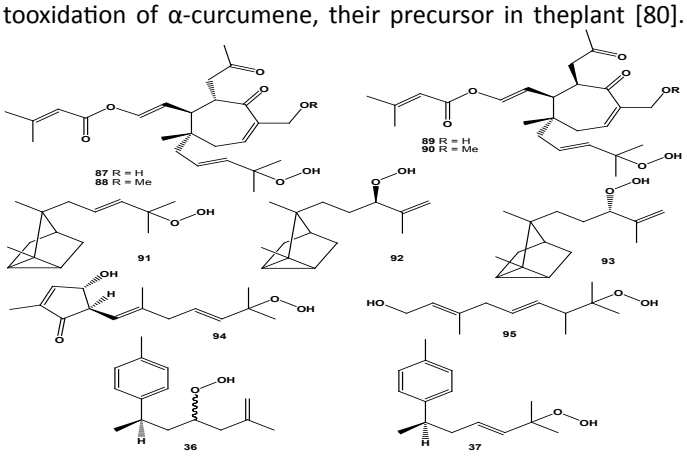
Seven-membered vibsane-type diterpene hydroperoxides named 5-epi-vibsanin K (87), 18-O-methyl-5-epi-vibsanin K (88) as well as their corresponding C-5 epimers (89) and (90) have been isolated from the leaves of Viburnum awabuki (syn: Viburnum odoratissimum var. arboricola;family Adoxaceae, Caplifoliaceae). The occurrence of these seven-membered vibsane-type diterpenes with a cis relationship on the C-5 and C-10 positions in nature have been predicted by conformational analysis of vibsanin B, an eleven-membered vibsane-type diterpene. Some compounds exhibited moderate cytotoxic activities on KB cells [70,71].

Several santalane and isocampherenane sesquiterpenes, including three isomeric sesquiterpene hydroperoxides (91-93) have been isolated from Illicium tsangii(family Illiciaceae; a poisonous shrub from southern China used in traditional medicine for treating pain). The santalanes may be derived from (−)-□-santalene by oxidation reactions [72,73].



Anti-HIV and cytotoxic activities of litseaverticillolA isolated from the twigs and leaves of shrubLitsea verticillata(Lun Ye Mu Jiang Zi in Chinese;the roots and leaves are used medicinally for treating rheumatism and relieving menstrual cramping and soreness) are known [74]. Synthesis of litseaverticillols B, E (94), I, and J as well as the structural reassignment of litseaverticillol E (94) have been achieved by means of a biomimetic sequence of transformations during which a [4 + 2]-initiated reaction cascade and an ene reaction, both involving singlet oxygen [(1)O(2)], formed key steps. The reassignment of the structure of litseaverticillol E to include an allylic hydroperoxide provides strong support for biogenetic hypothesis was reported [75].

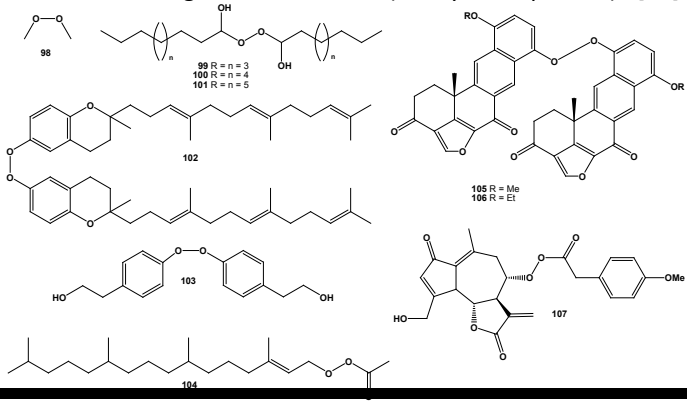
Compound (95) was isolated from a multi-branched shrub Heterothalamus alienus (family Asteraceae; it used in Brazilian and Argentinean folk medicine)[76]. Senecio species are used for therapeutic purposes, including the treatment of fungal skin infections [77], antiseptic [78], and pneumonia [79].The fresh aerial parts of Senecio selloi (family Asteraceae) contains two hydroperoxides (96 and 97), which wereidentified indirectly by isolation, identification and posterior photooxidation of α-curcumene, their precursor in theplant [80].



Rareacyclic peroxides

Acyclic peroxides differ the other two types of peroxides: a) hydroperoxides and b) endoperoxides by the presence of the peroxy (-O-O-)linkagebetween the fragments of the same and/or other molecular structure. This bridge on the chemical structures marked in green. Several compoundswere found in nature. Dimethyl peroxide (98) was detected among the volatile components of Basella rubra (family Basellaceae)[81], and three other acyclic bis(1-hydroxyalkyl)peroxides (99–101)in the essential oil of Japanese citrusfruit, Citrus iyo(iyokan, also known as anadomikan)[82,83]. Extract of the Brazilian medicinal plantKielmeyera coriacea (family Clusiaceae) afforded a δ-tocotrienol peroxy-dimer (102) [84], other peroxide dimer named bungein A (103) was found in the aerial parts of themedicinal plant Clerodendrum bungei (also known as Mexicali Rose, Mexican Hydrangea and/or Cashmere Bouque) [85]. Leucoperoxyterpene (104)with good antibacterial activity hasbeen isolated from extract of aerial parts of the medicinal plant Leucosceptrumcanum (family Laminaceae) [86].

Dimeric dihalenaquinolides A (105)and B (106), from marine origin, have an peroxidelinkage between two meroterpenoid units [87]. Lactucin-8-O-p-methoxyphenyl acetate (107), a cytotoxic sesquiterpene lactone,has been detected inMulgedium tataricum(family Compositae) [88].



Conclusion

During the last 40 years, there has been anunprecedented growth in the chemistry of natural as well as synthetic peroxides.Currently, the rapid progress in chemistry of organic peroxidesis to a large degree determined by their high biological activity.In medicinal chemistry of peroxides, particular emphasis isgiven to the design of compounds having activity againstcausative agents of malaria and human helminth infections.In medicinal chemistry ofperoxides, for example, ascaridole and artemisinin a natural peroxides exhibiting high antimalarialactivity, is the most important drug in use for approximately40 years [1-5,8,9,89-93].This review also emphasizes the role of hydroperoxides fromfungi, fungal endophytes, algae, plants, lichens, and bryophytes as animportant source of leads for drug discovery.

References

[1] Dembitsky V.M. Bioactive peroxides as potential therapeutic agents. Eur. J. Med. Chem., 2008,43, 223-251.

[2] Dembitsky V.M., Gloriozova T., Poroikov V.V. Natural peroxy anticancer agents. MiniRev. Med. Chem., 2007, 7, 571-589.

[3] Casteel D.A. Peroxy natural products. Nat. Prod. Rep., 1992,9, 289-312.

[4] Casteel D.A. Peroxy natural products. Nat. Prod. Rep.,1999,16, 55-73.

[5] Liu D.Z., Liu J.K. Peroxy natural products.Nat. Prod.Bioprospect.,2013, 3,161–206.

[6] Lange B.M., Ahkami A.Metabolic engineering of plant monoterpenes, sesquiterpenes and diterpenes-current status and future opportunities //Plant Biotechnol. J., 2013,11,169-196.

[7] Liu Q.M., Jiang J.G.Antioxidative activities of medicinal plants from TCM.Mini. Rev. Med. Chem., 2012, 12,1154-1172.

[8] Terent'ev A.O., Borisov D., Vil V.A., Dembitsky V.M. Synthesis of five- and six-membered cyclic organic peroxides: key transformations into peroxide ring-retaining products. Beilstein J. Org. Chem., 2014,10, 34-114.

[9] Jung M., Kim H., Lee K., Park M.Naturally occuring peroxides with biological activities.Mini Rev. Med. Chem., 2003, 3,159-165.

[10] Sun Y., Zhao Z., Feng Q., Xu Q., Lue L., Liu J.-K., Zhang L., Wu B., Li Y.-Q.Unusual spirodecane sesquiterpenes and a fumagillol analog from Cordyceps ophioglossoides.Helv.Chim. Acta,2013, 96, 76-84.

[11] Ding L., Maier A., Fiebig H.-H., Lin W.-H., Peschel G., Hertweck C.Kandenols A-E, eudesmenes from an endophytic Streptomyces sp. of the mangrove tree Kandelia candel.J. Nat. Prod., 2012, 75, 223-227.

[12] Weiser J., Matha V., Jegorov A. Tolypocladium terricola sp. N., a new mosquito-killing species of the genus Tolypocladium Gams (Hyphomycetes).Folia Parasitol. (Prague), 1991,38, 363-369.

[13] Sedmera P., Halicek V., Jegorov A., Serge A.L. Cyclosporin D hydroperoxide a new metabolite of Tolypocladium terricola. Tetrahedron Lett., 1995, 36,6953–6956.

[14] Wang G.-J., Liang W.-L., Ju Y.-M., Yang W.-B., Chang Y.-W., Lee T.-H.Inhibitory effects of terpenoids from the fermented broth of the ascomycete Stilbohypoxylon elaeicola YMJ173 on nitric oxide production in RAW264.7 macrophages.Chem. Biodiver., 2012, 9,131-138.

[15] Erb-Downward J.R., Noggle R.M., Williamson P.R., Huffnagle G.B.The role of laccase in prostaglandin production by Cryptococcus neoformans.Mol. Microbiol., 2008, 68, 1428-1437.

[16] Wang F.Z., Fang Y.C., Zhu T.J., Zhang M., Lin A.Q., Gu Q.Q., Zhu W.M.Seven new prenylated indole diketopiperazine alkaloids from holothurian-derived fungus Aspergillus fumigatus. Tetrahedron,2008, 64, 7986-7991.

[17] Zheng W., Liu T., Xiang X., Gu Q. Sterol composition in field-grown and cultured mycelia of Inonotus obliquus.Yaoxue Xuebao, 2007, 42, 750-756.

[18] Fusetani N., Hashimoto K.Diethyl peroxides. Probably responsible for mozuku poisoning. Bull. Jpn. Soc. Sci. Fish, 1981, 47, 1059-1063.

[19] Ikawa M., Sasner J.J., Haney J.F. Activity of cyanobacterial and algal odor compounds found in lake waters on green alga Chlorella pyrenoidosa growth.Hydrobiologia, 2001,443, 19-22.

[20] Howard B.M., Fenical W., Finer J., Hirotsu K., Clardy J.Neoconcinndiol hydroperoxide, a novel marine diterpenoid from the red alga Laurencia. J. Am. Chem. Soc., 1977,99, 6440–6441.

[21] Yu X.-Q., He W.-F., Liu D.-Q., Feng M.-T., Fang Y., Wang B., Feng L.-H., Guo Y.-W., Mao S.-C. A seco-laurane sesquiterpene and related laurane derivatives from the red alga Laurencia okamurai Yamada. Phytochemistry, 2014, 103, 162-170.

[22] Ji N.Y., Li X.-M., Li K., Ding L.-P., Gloer J.B., Wang B.-G.Laurendecumallenes A–B and laurendecumenynes A–B, halogenated nonterpenoid C15-acetogenins from the marine red alga Laurencia decumbens.Nat. Prod., 2007, 70, 1499–1502.

[23] Teasdale M.E., Shearer T.L., Engel S., Alexander T.S., Fairchild C.R., Prudhomme J., Torres M., Le Roch K., Aalbersberg W., Hay M.E., Kubanek J.Bromophycoic acids: Bioactive natural products from a Fijian red alga Callophycus sp.J. Org. Chem., 2012, 77, 8000-8006.

[24] Kolesnikova S.A., Lyakhova E.G., Kalinovsky A.I., Dmitrenok P.S., Dyshlovoy S.A., Stonik V.A.Diterpenoid hydroperoxides from the Far-Eastern brown alga Dictyota dichotoma.Aust. J. Chem., 2009, 62, 1185-1188.

[25] Fernández J.J., Souto M.L., Gil L.V., Norte M.Isolation of naturally occurring dactylomelane metabolites as Laurencia constituents.Tetrahedron, 2005,61, 8910-8915.

[26] Qin J.J., Jin H.Z., Zhu J.X., Fu J.J., Hu X.J., Liu X.H., Zhu Y., Yan S.K., Zhang W.D.Japonicones E-L, dimeric sesquiterpene lactones from Inula japonica Thunb. Planta Med., 2010, 76, 278-283.

[27] Zhu J.X., Qin J.J., Jin H.Z., Zhang W.D.Japonicones Q–T, four new dimeric sesquiterpene lactones from Inula japonica Thunb. Fitoterapia, 2013,84, 40-46.

[28] Boonprab K., Matsui K., Akakabe Y., Yotsukura N., Kajiwara T.Arachidonic acid conversion by lipoxygenase in the brown alga, Laminaria angustata.Kasetsart J. Nat. Sci., 2004, 38, 72-77.

[29] Akakabe Y., Matsui K., Kajiwara T. Enantioselective 2-hydroperoxylation of long-chain fatty acids in marine algae. Fish Sci., 2001, 67, 328-332.

[30] Nowicka B., Kruk J.Plastoquinol is more active than α-tocopherol in singlet oxygen scavenging during high light stress of Chlamydomonas reinhardtii.Biochim.Biophys. Acta, Bioenerget., 2012, 1817, 389-394.

[31] Sabry O.M.M., Andrews S., McPhail K.L., Goeger D.E., Yokochi A., LePage K.T., Murray T.F., Gerwick W.H.Neurotoxic meroditerpenoids from the tropical marine brown alga Stypopodium flabelliforme.J. Nat. Prod., 2005, 68, 1022-1030.

[32] Morita M., Ohno O., Suenaga K.Biselyngbyolide A, a novel cytotoxic macrolide from the marine cyanobacterium Lyngbya sp.Chem. Lett., 2012, 41, 165-167.
[33] Morita M., Ohno O., Teruya T., Yamori T., Inuzuka T., Suenaga K.Isolation and structures of biselyngbyasides B, C, and D from the marine cyanobacterium Lyngbya sp., and the biological activities of biselyngbyasides.Tetrahedron, 2012,68,5984–5990.
[34] Kumar S.S., Jayendra K.Cytotoxity of marine algal steroids in HeLa cells - 2D & 3D QSAR approach.Int. J. Pharm. Bio. Sci., 2012,3, 204-212.
[35] Permeh P., Saeidnia S., Mashinchian-Moradi A., Gohari A.R. Sterols from Sargassum oligocystum, a brown algae from the Persian Gulf, and their bioactivity.Nat. Prod. Res., 2012, 26, 774-777.
[36] Wang W., Li H., Wang Y., Xia X., Okada Y., Okuyama T.Chemical constituents from brown alga Sargassum fusiforme.Zhongcaoyao, 2008,39, 657-661.
[37] Lo J.-M., Wang W.-L., Chiang Y.-M., Chen C.-M.Ceramides from the Taiwan red alga Ceratodictyon spongiosum and symbiotic sponge Sigmadocia symbiotica.J. Chinese Chem. Soc. (Taipei, Taiwan), 2001, 48, 821-826.
[38] Qi S.-H., Zhang S., Huang J.-S., Xiao Z.-H., Wu J., Long L.-J. Glycerol derivatives and sterols from Sargassum parvivesiculosum.Chem. Pharm. Bull., 2004, 52, 986-988.
[39] Dembitsky V.M., Řezanková H., Řezanka T., Hanuš L.O.Variability of the fatty acids of the marine green algae belonging to the genus Codium.Biochem. Syst. Ecol., 2003, 31, 1125-1145.
[40] He Z., Zhang A., Ding L., Lei X., Sun J., Zhang L.Chemical composition of the green alga Codium divaricatum Holmes. Fitoterapia, 2010, 81, 1125-1128.
[41] Sheu J.-H., Liaw C.-C., Duh C.-Y. Oxygenated clerosterols isolated from the marine alga Codium arabicum. J.Nat. Prod., 1995, 58, 1521–1526.
[42] Moghaddam F.M., Farimani M.M., Seirafi M., Taheri S., Khavasi H.R., Sendker J., Proksch P., Wray V., Edrada R.A.Sesterterpenoids and other constituents of Salvia sahendica.J. Nat. Prod., 2010, 73, 1601-0165.
[43] Uchiyama N., Matsunaga K., Kiuchi F., Honda G., Tsubouchi A., Nakajima-Shimada J., Aoki T.Trypanocidal terpenoids from Laurus nobilis L.Chem. Pharm. Bull., 2002, 50, 1514-1516.
[44] Otoguro K., Iwatsuki M., Ishiyama A., Namatame M., Nishihara-Tukashima A., Kiyohara H., Hashimoto T., Asakawa Y., Omura S., Yamada H.In vitro antitrypanosomal activity of plant terpenes against Trypanosoma brucei.Phytochemistry, 2011,72, 2024-2030.
[45] Taglialatela-Scafati O., Pollastro F., Cicione L., Chianese G., Bellido M.L., Munoz E., Ozen H.C., Toker Z., Appendino G.STAT-3 Inhibitory bisabolanes from Carthamus glaucus.J. Nat. Prod., 2012,75, 453-458.
[46] Asada Y., Sukemori A., Watanabe T., Malla K.J., Yoshikawa T., Li W., Kuang X., Koike K., Chen C.-H., Akiyama T., Qian K., Nakagawa-Goto K., Morris-Natschke S.L., Lu Y., Lee K.-H. Isolation, structure determination, and anti-HIV evaluation of tigliane-type diterpenes and biflavonoid from Stellera chamaejasme.J. Nat. Prod., 2013, 76,852-857.
[47] Aboushoer M.I., Fathy H.M., Abdel-Kader M.S., Goetz G., Omar A.A. Terpenes and flavonoids from an Egyptian collection of Cleome droserifolia.Nat. Prod. Res., 2010, 24, 687-696.
[48] Fattorusso E., Santelia F.U., Appendino G., Ballero M., Taglialatela-Scafati O.Polyoxygenated eudesmanes and trans-chrysanthemanes from the aerial parts of Santolina insularis.J. Nat. Prod., 2004, 67, 37-41.
[49] Cherchi G., Deidda D., De Gioannis B., Marongiu B., Pompei R., Porcedda S. Extraction of Santolina insularis essential oil by supercritical carbon dioxide: influence of some process parameters and biological activity.Flavour.Fragr. J., 2001, 16,35-43.
[50] Lee S.O., Choi S.Z., Choi S.U., Kim G.H., Kim Y.C., Lee K.R.Cytotoxic terpene hydroperoxides from the aerial parts of Aster spathulifolius.Arch. Pharm. Res., 2006, 29, 845-848.
[51] Wang W.-S., Li E.-W., Jia Z.-J.Terpenes from Juniperus przewalskii and their antitumor activities.Pharmazie, 2002, 57, 343-345.
[52] Dembitsky V.M. Lipids of Bryophytes. Prog. Lipid Res., 1993, 32, 281-356.
[53] Becker H., Martini U.Studies on the chemistry and biology of mosses, No. 140.Terpenoids from the in vitro cultured liverwort Riella helicophylla.Zeitsch.Naturfor. C: J. Biosci., 1999, 54, 997-1004.
[54] Li Y., Wang Z., Zhang M., Luo S., Chen J.Study on the terpene compounds from Ligularia kanaitzensis.J. Chinese Pharm. Sci., 2002, 11, 115-117.
[55] Sakunpak A., Matsunami K., Otsuka H., Panichayupakaranant P.Isolation of new monoterpene coumarins from Micromelum minutum leaves and their cytotoxic activity against Leishmania major and cancer cells.Food Chem., 2013, 139, 458-463.
[56] Song Q.-Y., Jiang K., Zhao Q.-Q., Gao K., Jin X.-J., Yao X.-J. Eleven new highly oxygenated triterpenoids from the leaves and stems of Schisandra chinensis.Org. Biomol. Chem., 2013, 11, 251-258.
[57] Graziose R., Rathinasabapathy T., Lategan C., Poulev A., Smith P.J., Grace M., Lila M.A., Raskin I.Antiplasmodial activity of aporphine alkaloids and sesquiterpene lactones from Liriodendron tulipifera L.J. Ethnopharm., 2011, 133, 26-30.
[58] Julianti E., Jang K.H., Lee S., Lee D., Mar W., Oh K.-B., Shin J.Sesquiterpenes from the leaves of Laurus nobilis L.Phytochemistry, 2012, 80, 70-76.
[59] Zhang M., Iinuma M., Wang J.-S., Oyama M., Ito T., Kong L.-Y. Terpenoids from Chloranthus serratus and their anti-inflammatory activities.J. Nat. Prod., 2012, 75, 694-698.
[60] Yodsaoue O., Sonprasit J., Karalai C., Ponglimanont C., Tewtrakul S., Chantrapromma S. Diterpenoids and triterpenoids with potential anti-inflammatory activity from the leaves of Aglaia odorata.Phytochemistry, 2011, 76, 83-91.
[61] Sripisut T., Ritthiwigrom T., Promgool T., Yossathera K., Deachathai S., Phakhodee W., Cheenpracha S., Laphookhieo S.Glycopentaphyllone: The first isolation of hydroperoxyquinolone from the fruits of Glycosmis pentaphylla.Phytochemistry Lett., 2012, 5, 379-381.
[62] Shiu W.K.P., Rahman M.M., Curry J., Stapleton P., Zloh M., Malkinson J.P., Gibbons S.Antibacterial acylphloroglucinols from Hypericum olympicum.J. Nat. Prod., 2012, 75, 336-343.
[63] Whitson E.L., Thomas C.L., Henrich C.J., Sayers T.J., McMahon J.B., McKee T.C. Clerodane diterpenes from Casearia arguta that act as synergistic TRAIL sensitizers.J. Nat. Prod., 2010, 73, 2013-2018.
[64] Pacheco A.G., Machado de Oliveira P., Pilo-Veloso D., Alcantara A.F.C.13C-NMR data of diterpenes isolated from Aristolo-

chia species,Molecules, 2009, 14, 1245-1262.
[65] Lopes L.M.X., Bolzani V.S., Trevisan L.M.V. Clerodane diterpenes from Aristolochia species. Phytochemistry, 1987, 26, 2781-2784.
[66] Bomm M.D., Zukerman-Schpector J., Lopes L.M.X. Rearranged (4→2)–abeo-clerodane and clerodane diterpenes from Aristolochia chamissonis. Phytochemistry, 1999,50, 455-461.
[67] Ono M., Tsuru T., Abe H., Eto M., Okawa M., Abe F., Kinjo J., Ikeda T., Nohara T.Bisabolane-type sesquiterpenes from the aerial parts of Lippia dulcis. J. Nat. Prod., 2006, 69, 1417-1420.
[68] Jung C.M., Kwon H.C., Seo J.J., Ohizumi Y., MatsunagaK., Saito S., Lee K.R.Two new monoterpene peroxide glycosides from Aster scaber.Chem. Pharm. Bull., 2001,49, 912-914.
[69] Chen Y.L., Lan Y.H., Hsieh P.W., Wu C.C., Chen S.L., Yen C.T., Chang F.R., Hung W.C., Wu Y.C.Bioactive cembrane diterpenoids of Anisomeles indica. J. Nat. Prod., 2008, 71, 1207-1212.
[70] Minami H., Anzaki S., Kubo M., Kodama M., Kawazu K., Fukuyama Y.Structures of new seven-membered ring vibsane-type diterpenes isolated from leaves of Viburnum awabuki.Chem. Pharm. Bull., 1998, 46, 1194-1198.
[71] Fukuyama Y., Minami H., Matsuo A., Kitamura K., Akizuki M., Kubo M.Seven-membered vibsane-type diterpenes with a 5,10-cis relationship from Viburnum awabuki. Chem. Pharm. Bull. (Tokyo), 2002,50,368-371.
[72] Ngo K.S., Brown G.D.Allohimachalane, seco-allohimachalane and himachalane sesquiterpenes from Illicium tsangii. Tetrahedron, 1999, 55, 759-770.
[73] Ngo K.S., Brown G.D.Santalane and isocampherenane sesquiterpenoids from Illicium tsangii. Phytochemistry, 1999,50, 1213-1216.
[74] Zhang H.-J., Tan G.T., Hoang V.D., Van Hung N., Cuong N.M., Soejarto D.D., Pezzuto J.M., Fong H.H.S. Natural anti-HIV agents. Part 2: Litseaverticillol A, a prototypic litseane sesquiterpene from Litsea verticillata. Tetrahedron Lett., 2001, 42, 8587–8591.
[75] Vassilikogiannakis G., Margaros I., Montagnon T.Biomimetic total synthesis of litseaverticillols B, E, I, and J and structural reassignment of litseaverticillol E.Org. Lett., 2004,10,2039-2042.
[76] Huber H., Frohlke E.A new spray-reagent for the detection and quantitative estimation of peroxides. Chromatographia, 1972, 5, 256-257.
[77] Portillo A., Vila R., Freixa B., Adzet T., Cañigueral S.Antifungal activity of Paraguayan plants used in traditional medicine.J. Ethnopharm., 2001,76, 93-98.
[78] Bah M., Bye R., Pereda-Miranda R. Hepatotoxic pyrrolizidine alkaloids in the Mexican medicinal plant Packera candidissima (Asteraceae: Senecioneae).J. Ethnopharm., 1994, 43, 19-30.
[79] Hammond G.B., Fernández I.D., Villegas L.F., Vaisberg A.J.A survey of traditional medicinal plants from the Callejón de Huaylas, Department of Ancash, Perú.J. Ethnopharm., 1998,61, 17-30.
[80] Rücker G., Manns D., Schenkel E.P., Hartmann R., Heinzmann B.M. Sesquiterpene peroxides from Senecio selloi.Phytochemistry, 1999,52, 1587-1591.
[81] Kameoka H., Kubo K., Miyazawa M.Volatile flavor components of malabar-nightshade (Basella rubra L.).J. Food Comp. Anal., 1991, 4, 315-321.
[82] Hiroi M., Takaoka D. Studies on the peel oil of Citrus iyo. Nippon Kagaku Kaishi, 1973, 11, 1339-1341.
[83] Kobayashi A., Nohara K., Ohsumi E., Yamanishi T.Identification of di(l-oxyalkyl)-peroxides in the essential oil of Citrus iyo. Agric. Biol.Chem., 1990, 54, 561-567.
[84] De Mesquita M.L., Araújo R.M., Bezerra D.P., Filho R.B., de Paula J.E., Silveira E.R., Pessoa C., de Moraes M.O., Lotufo L.V.C., Espindol L.S. Cytotoxicity of δ-tocotrienols from Kielmeyera coriacea against cancer cell lines.Bioorg. Med. Chem., 2011, 19, 623–630.
[85] Yang H., Hou A.J., Mei S.X., Sun H.D., Che C.T. Constituents of Clerodendrum bungei.J.Asian Nat. Prod. Res., 2002, 4, 165-169.
[86] Devkota K.P., Lenta B.N., Wansi J.D., Sewald N. Antibacterial constituents from Leucosceptrum canum.Phytochemistry-Lett.,2010, 3, 24-28.
[87] Shen Y.C., Prakash C.V.S., Guh J.H. New pentacyclic polyketide dimeric peroxides from a Taiwanese marine sponge Petrosia elastic.Tetrahedron Lett., 2004,45, 2463-2466.
[88] Wang X.X., Lin C.J., Jia Z.J.Triterpenoids and Sesquiterpenes from Mulgedium tataricum.Planta Med.,2006, 72, 764-767.
[89] Dembitsky V.M. Chemistry and biodiversity of biologically active natural glycosides. Chem. Biodiver., 2004, 1, 673-781.
[90] Youns M., Hoheisel J.D., Efferth T. Traditional Chinese medicines (TCMs) for molecular targeted therapies of tumours.Curr. Drug Discov. Technol.,2010, 7, 37-45.
[91] Angus B. Novel anti-malarial combinations and their toxicity. Expert Rev. Clin.Pharmacol., 2014, 7, 299-316.
[92] Farhi M., Kozin M., Duchin S., Vainstein A. Metabolic engineering of plants for artemisinin synthesis. Biotechnol.Genet. Eng. Rev., 2013, 29, 135-148.
[93] Pastre J.C., Browne D.L., Ley S.V. Flow chemistry syntheses of natural products. Chem.Soc. Rev.,2013, 42, 8849-8869.