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Astonishing Diversity of Natural Peroxides as Potential Therapeutic Agents

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Abstract

Peroxides *are an interesting group among* biological active natural compounds. *These metabolites contain* a *peroxide group* (-O-O-) in which each oxygen atom is bonded to the other oxygen and to another atom. β-Oxygen in hydro*peroxide group* is considered as more active. Present review describes research on more than 230 natural peroxides isolated from plants, algae, and fungi. Intensive searches for new classes of biologically active metabolites produced by terrestrial and marine origin have resulted in the discovery of dozens of compounds possessing high antimalarial, antibacterial, cytotoxic, and other pharmacological activities as an important source of leads for drug discovery.

Keywords: Peroxides; Plants; Algae; Fungi; Pharmacological activities

Introduction

More than 1,000 peroxides (hydro-, endo-, and, also acyclic) 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 [6-8]. The purpose of this review is to summarize bioactive metabolites of more than 230 natural peroxides, belonging to diverse structural classes: terpenes, steroids, alkaloids, fatty acids, and other compounds.

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

Fungal Peroxides

Hydroperoxides

Mono (or di-) substituted natural products of hydrogen peroxide (dioxidane, HOOH), having the skeleton ROOH (Figure 1), in which R is any organic group(s), called generically as hydroperoxides and are named substitutively by citing the prefix hydroperoxy, and/or peracid(s), respectively. Many different natural hydroperoxides have been isolated from fungi, algae, plant, invertebrates, and animal sources [1-5,9].

Unusual spiro [4.5] decane sesquiterpenes, cordycepol A, B and C (1) (Figure 2), were isolated from the cultured mycelia of parasitic fungi *Cordyceps ophioglossoides* (family Ophiocordycipitaceae). Isolated compounds showed the cytotoxic activities (IC_{50} values in the range of 12-33 μg/mL) against HeLa and HepG2 [10].

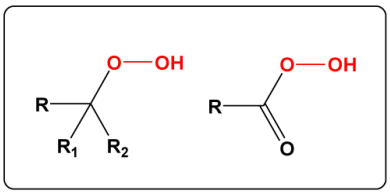

Figure 1: Common structures of mono-hydro peroxide and per-acids (the peroxide group is marked in red). R, R1 and R2 mark hydrocarbon moieties.

Eudesmene-type sesquiterpenes, kandenols C (2) and D (3), have been isolated from Streptomyces sp. HKI0595 derived from the mangrove plant *Kandelia candel* as 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 neoformans* was used for production of several species of prostaglandins (PGE2, PGH2 and 15-keto-PGE2) from arachidonic acid, and including unusual endo- and hydroperoxide PGG2 (6) [15].

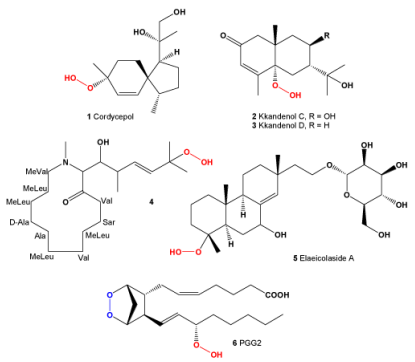

Figure 2: Several fungal hydroperoxides belonging to different classes of natural compounds.

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].

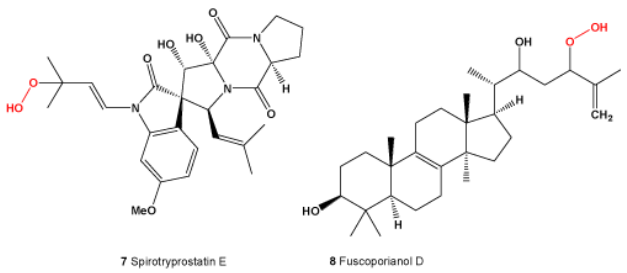

Figure 3: Fungal hydroperoxides from *Aspergillus fumigatus* and mycelia of *Inonotus obliquus*.

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].

Endoperoxides: Natural products having the skeleton ROOR1, in which R is any organic group(s), called generically as endoperoxides. A lot of different types (Figure 4) natural endoperoxides have been isolated from fungi, algae, plants, and other sources [1-5,9].

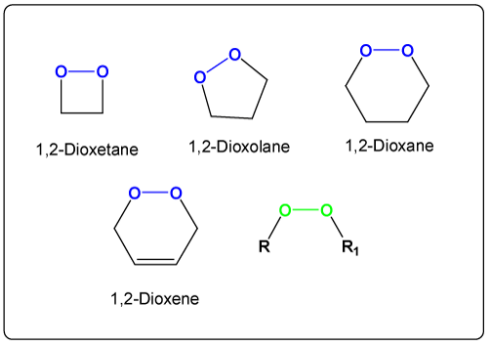

Figure 4: Common structures of endoperoxides four-membered (1,2-dioxetane), five-membered (1,2-dioxolanes), six-membered (1,2-dioxanes and 1,2-dioxenes), and seven- and more membered endoperoxides (the peroxide group is marked in blue). Acyclic peroxides, R and R1 marked in green.

Several nor-sesquiterpene peroxides (Figure 5), named as talaperoxide A (9), B (10), C (11), and D (12), were isolated from culture of fungi *Talaromyces* sp. HN21-3C (family Trichocomaceae). Isolated compounds showed antineoplastic activity against mammary cancer, prostatic carcinoma, uterine cervix carcinoma or hepatic carcinoma [18,19]. Same compounds, talaperoxides A-D (9-12), as well as one known analog, steperoxide B (14, or merulin A), have been isolated from a mangrove endophytic fungus, *Talaromyces flavus* [20]. Talaperoxides (11) and (12) showed cytotoxicity against the five human cancer cell lines with IC50 values between 0.70 and 2.78 μg/mL.

Chamigrane-type metabolites named steperoxides A (13), B (14), C (15) and D (16) were isolated from the hydnoid fungus *Steccherinum ochraceum* (family Phanerochaetaceae). Compounds (15 and 16) showed significant antimicrobial activity against *Staphylococcus aureus* at 10 and 5 μg/disk [21-23]. Semi-synthetic derivative (17) of the fugally-derived natural product (11) showed the antiparasitic and cytotoxic activity (IC50=0.043 μM vs. *T. brucei*; IC_{50}=13 μM vs. Hela cells), respectively [24].

Previously, the same nor-chamigrane endoperoxide, named as merulin A (syn. steperoxide B, 15), B (19), C (18), and D (20), were isolated from the culture broth extract of an endophytic fungus of *Xylocarpus granatum*. Same compounds were isolated from the endophytic fungus *Talaromyces flavus* isolated from the mangrove plant *Sonneratia apetala* [20]. Compounds merulin A and C displayed significant cytotoxicity against human breast (BT474) and colon (SW620) cancer cell lines. Endophytic fungi have been the source of a wide range of structurally interesting and biologically active compounds. The endophytic fungus XG8D, which was isolated from the mangrove plant, *Xylocarpus granatum* (Meliaceae), as the EtOAc extract of this strain showed potent cytotoxic activity against human breast (BT474) and colon (SW620) cancer cell lines. The fungus strain XG8D was classified as a member of the family Meruliaceae (order Polyporales, subclass *Incertae sedis*, class Agaricomycetes, phylum Basidiomycota) from rDNA sequences and LUS phylogeny [25].

Cytosporolides A (21), B (22), and C (23), caryophyllene-derived meroterpenoids with a unique peroxylactone skeleton, were isolated from cultures of the fungus *Cytospora* sp. All cytosporolides showed

significant antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pneumoniae* [18]. Also, compound (23) showed good activity in vitro against dermatophytic fungi and moderate activity against *C. albicans* and *S. aureus*.

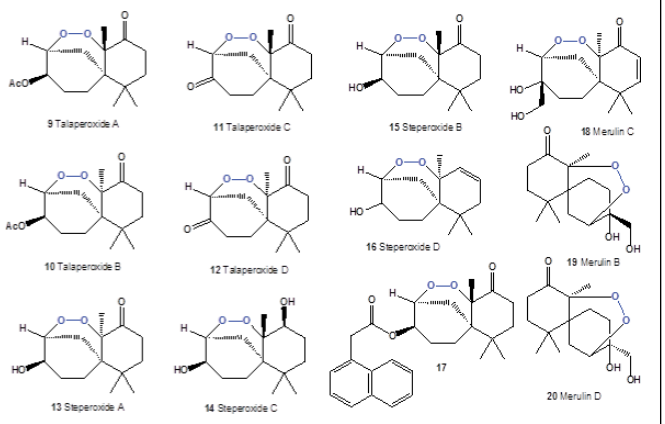

Figure 5: Fungal nor-sesquiterpene endoperoxides and derivatives.

Chloropupukeanolides A (24) and B (25), unprecedented spiroketal peroxides, two highly functionalized metabolites featuring a chlorinated pupukeanane core, were isolated from an endophytic fungus *Pestalotiopsis fici*. The compound (24) was reported to have anti-HIV and anti-cancer activities with an inhibitory effect on HIV-1 replication in C8166 cells of 6.9 micromolar (EC50 value) and IC50 values of 16.9, 15.5, and 15.9 μM against HeLa, MCF-7, and MDA-MB-231 cell lines, respectively [26].

Dimeric anthrone peroxide, named oxanthromicin (26), an antibiotic isolated from an *Actinomadura* sp. SCC 1646 fermentation broth [27,28]. Adxanthromycins A (27) and B (28) are new inhibitors of ICAM-1/LFA-1 mediated cell adhesion molecule isolated from the fermentation broth of Streptomyces sp. NA-148. Adxanthromycins A and B inhibited the formation of the JY cell aggregates from 1.5 mg/mL, respectively, in a dose-dependent manner. Components A and B also inhibited a human T cell leukemia cell line SKW-3 adhesion to soluble ICAM-1 in a dose-dependent manner with an IC50 of 18.8 and 25.0 μg/mL, respectively [29,30].

Hypocrellins are dark red pigments having the perylenequinone structure, with photodynamic activity toward microorganisms. These pigments produced by the fungus Hypocrella bambusae [31,32], and a parasitic fungus *Shiraia bambusicoia* [33-35]. All isolated metabolites have shown anticancer activities [33,36,37], and antiviral activity against the human immunodeficiency virus (HIV-1) [38]. Natural cytotoxic peroxyhypocrellin (29) was isolated from *S. bambusicoia* [34]. Stuctures showed in Figure 6.

Bioactive endoperoxide verruculogen [30] (Figure 7) for the first time was isolated from a strain of *Penicillium verruculosum* isolated from peanuts [39]. This compound (30) has also been isolated from a number of other microbiological sources including *Aspergillus caespitosus* [40], *A. fumigatus* [41], *A. fischeri* [42], *Penicillium piscarium* [43], *P. paxilli* [44], *P. piceum*, *P. nigricans*, *P. raistrickii* [43], *P. estinogenum* [45], *P. simplicissmum* [46], *Eupenicillium* sp. [47], and an invasive fungal pathogen *Neosartorya fischeri* (*A. fischerianus*) [48]. A tremorgenic mycotoxin verruculogen (30) is a potent inhibitor of high conductance Ca activated K (maxi-K) channel, other pharmacological effects of (30) have also been reported [49]. The acetoxy derivative (31) has been isolated from *Penicillium verruculosum* [50]. Other endoperoxide, fumitremorgin A (32), was recovered from a strain of *Aspergillus fumigatus* [51,52]. Fumitremorgin A (32) known as neurotropic metabolite [53] was produced by fungus *Aspergillus fumigatus* [54]. Diketopiperazine alkaloid, 13-oxoverruculogen (33), has been obtained from the fermentation of *Aspergillus fumigatus* from a holothurian, *Stichopus japonicus* (Lingshan Island, Qingdao, China) [55].

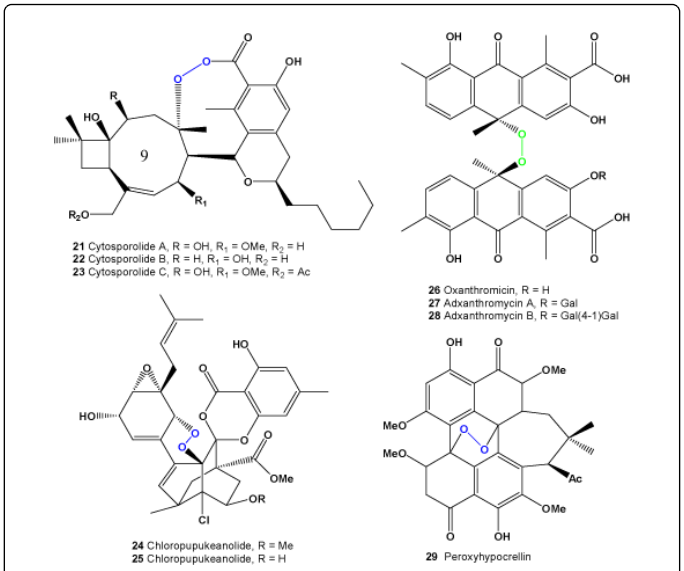

Figure 6: Fungal endo- and acyclic peroxides.

Asperversin A (34) and ergosterol peroxide (35) was obtained from the culture of *Aspergillus versicolor*, an endophytic fungus isolated from the marine brown alga *Sargassum thunbergii*. Compound exhibited antibacterial activities against Escherichia coli and *Staphyloccocus aureus* [56].

Ergosterol peroxide (35) (Figure 8) has been detected in many fungi and fungal endophytes: *Claviceps purpurea* (ergot fungus), *Ganoderma lucidum*, *G. tsugae* and *G. sichuanense* (lingzhi mushrooms) [2], mushroom *Daedalea quercina* [1], *Piptoporus betulinus* (known as the Birch bracket mushroom), *Cryptoporus volvatus* (known as the Grey-Brown Sap Rot mushroom) [2], *Guignardia laricina* (Botryosphaeriales), *Lampteromyces japonicus* (Moonlight mushroom, Australia) [1], a necrotrophic fungus *Botrytis cinerea* [2], *Lactarius uvidus* (North American milk-cap mushroom), *Lactarius volemus*, *Cryptoporus volvatus* (known as the Grey-Brown Sap Rot mushroom), *Aspergillus sp.*, *A. niger*, *A. oryzae*, *A. flavus*, *A. terreus*, and *A. fumigatus* [2], *Fusurium monilforme*, *F. osysporum*, *Penicillium rubrum*, *P. sclerotigenum* [1], *Dictyonema glabratum* (a lichen-forming basidiomycete), *Lasiosphaera nipponica*, *Gloeophyllum odoratum*, *Gymnopilus spectabilis*, *Hericium erinaceus* (medicinal, edible mushroom), *Hypsizigus marmoreus*, *Inonotus obliquus* (known as chaga mushroom), *Inonotus radiatus* (syn. *Mensularia radiata*), *Lenzites betulina* (birch mazegill or multicolor gill polypore fungus), fungus *Meripilus giganteus*, *Microporus flabelliformis* (syn. *Microporus affinis*), *Naematoloma fasciculare* (yellow mushroom syn. *Hypholoma fasciculare*), *Phellinus pini* (known as Red ring rot or White speck), *Phellinus ribis* (medicinal fungus), *Phellinus torulosus* (known as *Phellinus torulosus*),

Roseoformes subflexibilis (wood-rotting fungus), *Pyropolyporus fomentarius* (Syn. *Fomes fomentarius*), *Pisolithus tinctorius* (known in Europe as the Bohemian truffle), *Polyporus tuberaster*, and *Pseudephebe pubescens* (lichenized fungi within the Parmeliaceae family) [2], and from the edible mushroom, *Volvariella volvacea* [57].

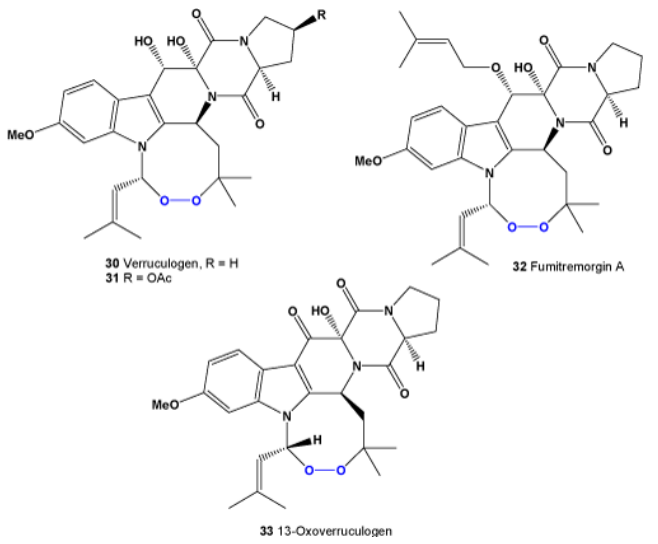

Figure 7: Some fungal eigth-membered endoperoxides.

Endophytic fungus No ZZF36 from a brown alga from the South China Sea, produced ergosterol peroxide (26), along with brassicaterol, and ergosterol [58].

The fruiting bodies of the edible mushroom *Gomphus clavatus* (family Gomphaceae) were collected from the wild and extracted with solvents of increasing polarity. Crude extracts were evaluated for their total phenolic content, their antioxidant capacity, and their cytotoxic activity against MCF-7 and PC-3 cancer cell lines. Ergosterol peroxide (26) was one of the most active constituents, with IC_{50} values of 35.8 μM and 30.6 μM for MCF-7 and PC-3 cells, respectively, suggesting that the cytotoxic activity of the crude extract could be at least partly attributed to the presence of ergostan derivatives. Those findings suggest that *G. clavatus* can be considered as a medicinal food with antioxidant and chemopreventive activities [59].

Ergosterol peroxide (26) was isolated from the ethanol extract of *Pleurotus eryngii*, an edible mushroom native to Mediterranean regions of Europe, the Middle East, and North Africa, as an inhibitor of osteoclast differentiation. This compound showed an inhibitory effect in a dose-dependent manner and an inhibition rate of up to 62% with low cytotoxicity, even at a concentration as low as 1.0 μg/mL [60]. Ergosterol peroxide (26) isolated from of the deep-sea derived fungus *Aspergillus sp.* CXCTD-06-6a showed activities against P388 and HeLa cell lines [61].

Ergosterol peroxide (26) have also been found in some lichenized ascomycetes: *Cetraria chlorophylla*, *C. islandica*, *Cladonia gracilis*, *Leioderma pycnophorum*, *Pseudocyphellaria encoensis* and *P. pluvialis*, *Lepolichen coccophorus*, *Lobaria pulmonaria*, *Ramalina hierrensis*, *R. tingitana*, *Rhizoplaca melanophthalma*, *Stereocaulon azoreum*, *Peltigera aphthosa* and *P. dolichorrhiza* [1,2].

Methanol extract of fungus Tremella fuciformis showed significant neuritogenic activity against PC12 cells. A neuritogenic compounds ergosterol peroxide (26) and 5α,8α-epidioxy-(22E,24R)-ergosta-6,22-diene-3β-ol 3-O-β-D-glucopyranoside (27) were isolated and identified from the methanol extract of fungus *T. fuciformis* [62]. Same compounds were isolated from the fruiting bodies of the Chinese toxic mushroom *Naematoloma fasciculare* [63]. Two peroxides (26 and 28) produced a camphor fungus *Antrodia camphorata* (known as Niu-Chang in Taiwan) [64]. Compound (28) obtained from the fruit bodies of mushroom *Boletus calopus* had weak antifungal action on a few pathogens, such as cucumber wilt disease fungus and wheat scab fungus [65].

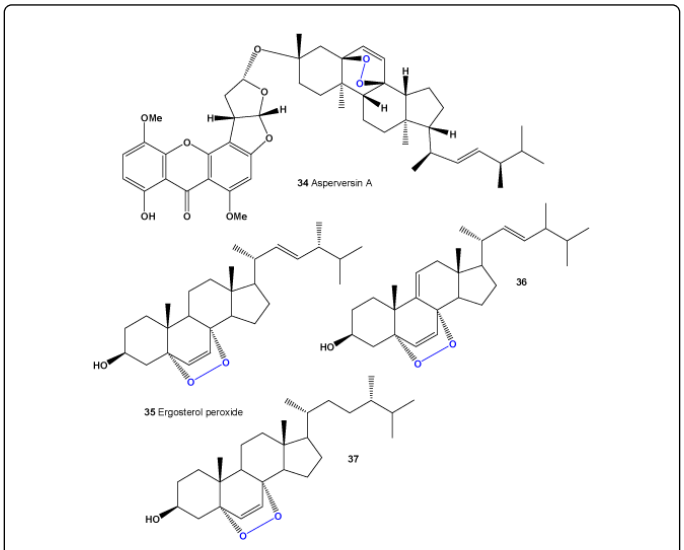

Figure 8: Some fungal ergosterol endoperoxides and derivatives.

Two sterols (31a and 32a) (Figure 9) were isolated from the fruiting body of *Panellus serotinus* also known as Mukitake mushroom (family Mycenaceae). Compound (31a) was also isolated from other edible mushroom Lepista nuda (also known as blewit, syn. *Clitocybe nuda*) [66]. Ergostane-type endoperoxy glycosides (33a and 34a) were isolated [67] from the ethanol extract of an attractive mushroom Lactarius volemus (family Russullaceae) which inhibits the growth of several tumor cell lines in vitro [68].

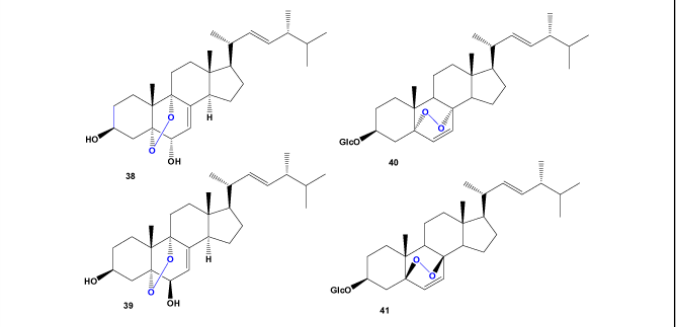

Figure 9: Fungal sterol endoperoxides.

Peroxides from algal species

Hydroperoxides: The (1-ethoxyethy1) hydroperoxide (41) was recovered from several algal species: two brown algae *Cladosiphon okamuranus*, *Analipus japonicus*, and red alga *Gracilariopsis chorda* (Gracilariaceae, Rhodophyta) [69]. Cumene hydroperoxide (42) was detected in green alga *Chlorella pyrenoidosa* [70].

The diterpenoid neoconcinndiol hydroperoxide (43) was found as a constituent of red alga *Laurencia snyderiae*. The suggestion was made that (43) arises from the brominated natural product concinndiol, also from L. snyderiae, by solvolytic ring contraction and oxygenation to yield the rearranged allylic hydroperoxide [71]. Laureperoxide (44), cuparene-derived sesquiterpene isolated from the red alga *Laurencia okamurai* (Nanji Island, China) [72]. Halogenated nonterpenoid C15-acetogenin, laurendecumenyne A (45) has been reported from the marine red alga *Laurencia decumbens*. Cytotoxicity against adenocarcinomic *human alveolar* basal *epithelial cells* A549 cells was showed [73].

Bioassay-guided fractionation of extracts from a Fijian red alga in the genus *Callophycus* sp. resulted in the isolation of five new compounds of the diterpene-benzoate class. Isolated bromophycoic acids A, B, C (46), 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 [74] (Figure 10).

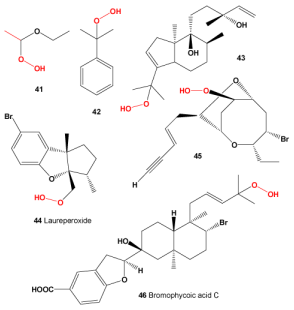

Figure 10: Algal hydroperoxides belonging to different classes of natural compounds.

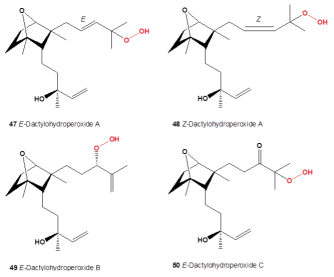

Figure 11: Hydroperoxides from brown algae.

Hydroperoxides have been found in the Russian population of brown alga, *Dictyota dichotoma* (Troitsa Bay, Sea of Japan, Russia), for example, dictyohydroperoxides A (E-47), A (Z-48), B (49) and C (50) [75] (Figure 11). Some isolated compounds showed moderate cytotoxicity against human cancer cell lines. Also, unstable hydroperoxide, dactylohydroperoxide C (50) produced by red algae *Laurencia* sp. from Tenefire (Canary Island) [76].

Two bioactive brominated diterpenes, cytotoxic bromoditerpene (51) and antibacterial bromoditerpene 2S-hydroperoxy-12R-hydroxy-isobromosphaerol (52) have been isolated from the marine red alga *Sphaerococcus coronopifolius* (also known as *Hematocelis fissurata*). The structure of the previously reported 12S-hydroxy-bromosphaerodiol (53) and 2S,12S-dihydroxyisobromo-sphaerol (54) were revised [77,78].

Several hydroperoxides as 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-eicosatetraenoic acids (55-57, respectively, Figure 12) by HPLC. These represented the mechanism of positional selectivity of LOX in this marine alga [79].

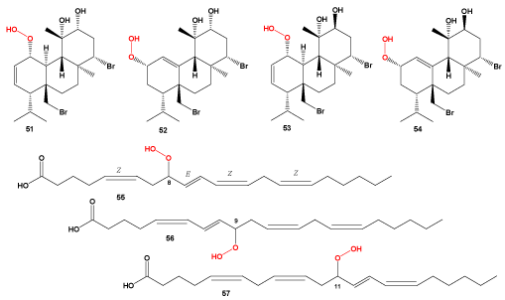

Figure 12: Hydroperoxides from marine red and brown algae.

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-hydroperoxy 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 [80].

Two bioactive compounds, dictyohydroperoxide (58) and hydroperoxy-acetoxycrenulide (59), 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 [75].

8a-hydroperoxy-α-tocopherone (60), 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) [81].

Several biological active meroditerpenoids stypohydroperoxide (61), 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 flabellinone possessed potent sodium channel blocking activity [82].

Marine cyanobacterium Lyngbya sp. led to the isolation of biselyngbyasides A, B, endo- peroxide biselyngbyaside C, and hydrobiselyngbyaside D (62), collected on Tokunoshima Island (Japan) [83,84]. Biselyngbyolide A exhibited strong apoptosis-inducing activity against HeLa S3 (human epithelial carcinoma *cell* line) and HL60 (human promyelocytic leukemia) cells [83]. Other 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 Ca^{2+} concentration in HeLa S3 cells [84]. Structures showed in Figure 13.

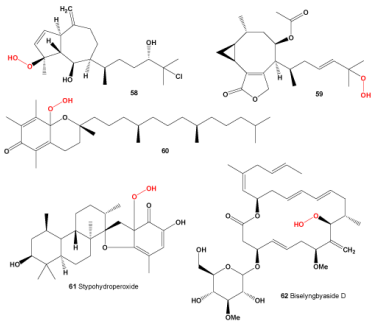

Figure 13: Algal hydroperoxides belonging to different classes of natural compounds.

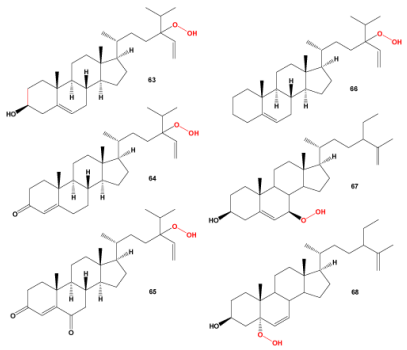

Figure 14: Sterol hydroperoxides from different algal species.

Cytotoxic steroids (63, 64 and 65) 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 [85]. Sterol, 24(R)-hydroxy-24-vinylcholesterol (63) has been isolated from *Sargassum oligocystum* (Heterokontophyta), which it is one of the most abundant algae distributed in the Persian Gulf [86], and in *Sargassum fusiforme* [87]. This compound (63) was also found in red alga *Ceratodictyon spongiosum* (Rhodymeniaceae) [88].

Several unusual glycerolipids, including at 24-ethylcholest-4,24(28)-dien-3β-ol, 24-vinylcholest-5-en-24ζ-hydroperoxy (66) were isolated from marine brown alga *Sargassum parvivesiculosum* [89].

Genus Codium contains a lot of different lipophylic metabolites [90], and sterols [91]. The two hydroperoxy clerosterols (67 and 68) were isolated from the the Indo-Pacific marine green alga *Codium arabicum* [92]. The compounds displayed significant cytotoxicity toward various cancer cell lines.

Ergosterol peroxide (35) has also been identified from some algal species: thus it was isolated from marine red alga *Laurencia cartilaginea* [93], brown alga *Turbinaria conoides* [94], green freshwater alga Chlorella vulgaris [95], and halotolerant alga *Dunaliella salina* [96] (Figure 14).

Endoperoxides: A few endoperoxides (Figure 15) have been isolated from algal species. Thus, the diastereomeric abietic acid endoperoxides (69) and (70) were isolated from freshwater *Elodea canadensis* [97], and endoperoxide biselyngbyaside C (71) produced by marine *Lyngbya* sp. [84].

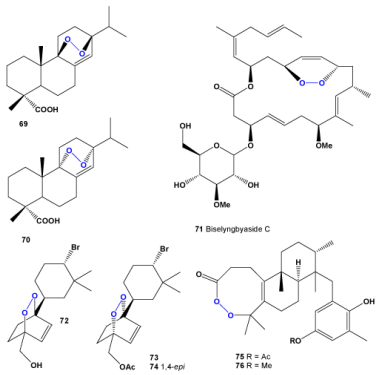

Figure 15: Endoperoxides from different marine algal species.

Several sesquiterpenes, majapolenes A (72), B, majapolone, and majapols A-D, were isolated from a Philippine collection of red alga *Laurencia majuscula*. With the exception of majapolene B, all compounds were isolated as inseparable diastereomeric mixtures. Majapolene A, a dioxabicyclo [2.2.2]-alkene, displayed modest activity in the NCI 60-cell line cytotoxicity screening. Majapolene A (72) was also found as a major component of a Philippine collection of *Laurencia caraibica* [98]. Similar majapolane sesquiterpenes with antibacterial activity, as isomeric mixture acetylmajapolene A, (73) and (74), have been found in an extract of an undescribed Malaysian (Pulau Tioman) species of the *Laurencia* genus [99]. Two diterpenoid peroxylactones, (75) and (76), were isolated from the brown seaweed *Taonia atomaria* [100].

Novel and bioactive peroxides from plant species

Hydroperoxides: Bioactive metabolite (77) (Figure 16) 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 [101].

A p-menthane hydroperoxide, (1R,4S)-1-hydroperoxy-p-menth-2-en-8-ol acetate (78), as trypanocidal agent against epimastigotes of *Trypanosoma cruzi*, was isolated from dried leaves of an aromatic evergreen tree *Laurus nobilis* (family Lauraceae) [102]. Plant metabolite (79) exhibited antitrypanosomal activity against *Trypanosoma brucei* [103].

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 (80) and (81). Isolated fucopyranosides are as potential 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 [104].

Interesting tigliane-type diterpenes, stelleracins A, B, C, D (82) and E (83), were isolated from the roots of a 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 [105] (Figure 16).

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 (82) (Figure 17) was isolated from the aerial parts of the herb *Cleome droserifolia* (syn. *Roridula droserifoli*) [106].

A trans-chrysanthemic monoterpenoid hydroperoxide (83) 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 [107]. The biological activity of *S. insularis* was also demonstrated against *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, *Candida tropicalis* and *Cryptococcus neoformans* [108].

Three sesquiterpene hydroperoxides (84-86), 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 (84) and (85), showed moderate cytotoxicity against human cancer cells with ED50 values ranging from 0.24 to 13.27 μg/mL [109].

Hydroperoxy terpene (87) 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 [110].

The lipophilic extract of the fresh water liverwort *Riella helicophylla* yielded several monoterpenes and diterpenes [111]. Several monoterpenes were hydroperoxides (90-93, 95 and 96) [112]. The 11-hydroperoxy-6,9-eremophiladien-8-one (94), along with oleanolic acid, β-amyrin, β-amyrin acetate and (+)-lupeol, were isolated from the EtOH extracts of *Ligularia kanaitzensis* (family Compositae) [113].

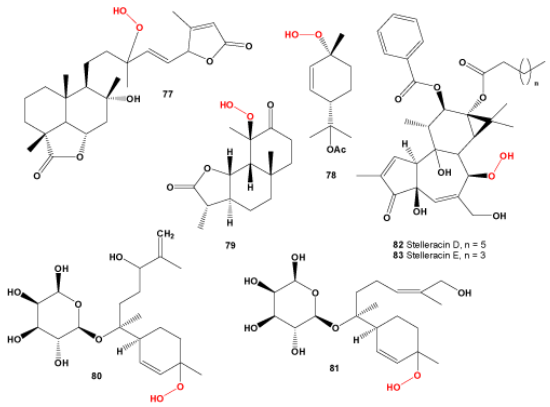

Figure 16: Plant hydroperoxides belonging to different classes of natural compounds.

Monoterpene coumarins, minutin A (97) and B (98) were purified from the 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 (77) 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 [114].

Eleven triterpenoids, schinchinenins A-H and schinchinenlactones A-C together with three known triterpenoids, henrischinins A-C, were isolated from the leaves and stems of *Schisandra chinensis* (also known as five flavor berry; native to forests of Northern China and the Russian Far East) by bioassay-guided fractionation. Schinchinenins E and F (99 and 100, Figure 18) 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 [115].

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The active constituents of bark and leaves of the traditionally used antimalarial plant *Liriodendron tulipifera* (known as the tulip tree, American tulip tree) by antiplasmodial-assay guided fractionation. Leaves yielded two known sesquiterpene lactones, peroxyferolide (101) and lipiferolide with antiplasmodial activity. The antiplasmodial activity of compound (101) (IC_{50}=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 [116].

Several sesquiterpenes, together with compounds (102) and (103) were isolated from leaves of an aromatic evergreen tree *Laurus nobilis*

(also known as Bay leaf). Most of these compounds exhibited moderate to significant cytotoxicity toward K562 leukemia cells [117].

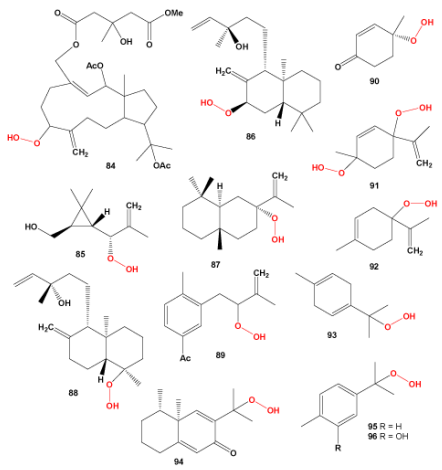

Figure 17: Plant hydroperoxides belonging to terpene, aroma and their derivatives.

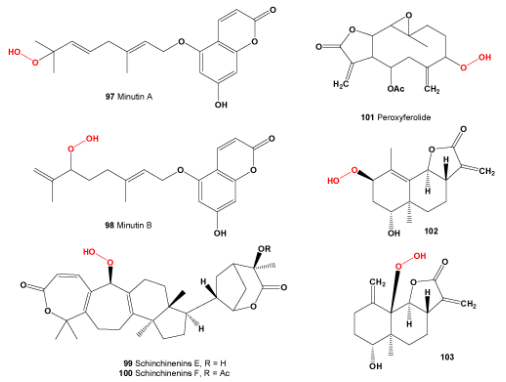

Figure 18: Plant hydroperoxides belonging to different classes of natural compounds

Lindenane sesquiterpenes, spicachlorantins A (104) and C (105) were isolated from the whole dicotyledonous plant 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 IC_{50} values of 0.22, 0.15, and 7.22 μM, respectively [118].

Several bioactive compounds, including (1R,3S,7E,11S,12R)-3-hydroperoxy-dolabella -4(16),7-dien-18-ol (106), was found in leaves extract of the oriental medicinal plant *Aglaia odorata* (family Meliaceae, known as Chinese perfume plant). All isolated compounds possessed potent nitric oxide inhibitory activity with IC_{50} values ranging from 2.1 to 14.2 μM, these being better than that of the positive control, indomethacin (IC_{50}=14.5 μM) [119].

A new hydroperoxyquinolone alkaloid, glycopentaphyllone (107) 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 [120].

Antibacterial acylphloroglucinols, named olympicins A, B, C, D (108), and (E) were isolated and characterized from the aerial parts of the flowering plant *Hypericum olympicum* cf. *uniflorum* (family Hypericaceae). All compounds exhibited min inhibitory concentrations (MICs) of 0.5 to 128 mg/L against *Staphylococcus aureus* strains [121] (Figure 19).

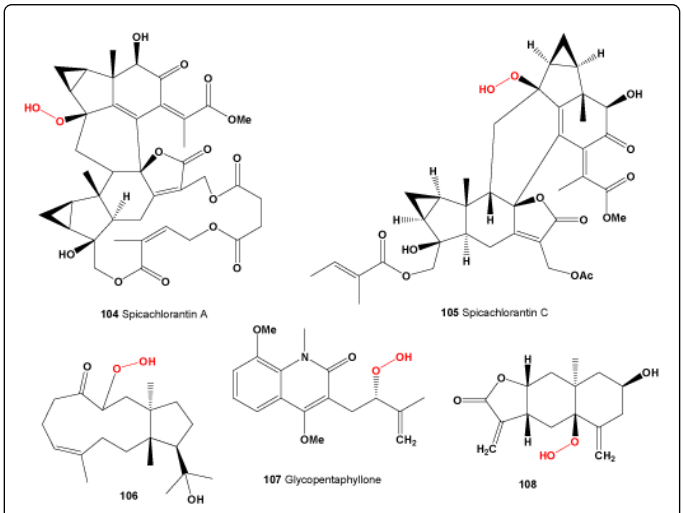

Figure 19: Plant antibacterial hydroperoxides.

Argutins A, B, C, D, E, F (109), G (110), and H (111) 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 ligand sensitizers [122]. Antibacterial acylphloroglucinols, named olympicins A, B, C, D (112), and (E) were isolated and characterized from the aerial parts of the plant *Hypericum olympicum* cf. uniflorum. All compounds exhibited min inhibitory concentrations (MICs) of 0.5 to 128 mg/L against *Staphylococcus aureus* strains [121].

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 [123]. Thus, clerodane diterpenoids isolated from Aristolochia species, compounds (113 and 114) (Figure 20) were isolated from *A. esperanzae* [124], and compound (115) was identified from *A. chamissonis* [125].

Six new bisabolane-type sesquiterpenes, peroxylippidulcines A-C (116-118) (Figure 21), peroxyepilippidulcine B, and epilippidulcines B and C, have been isolated from the aerial parts of *Lippia dulcis* (perennial herb; native to southern Mexico), along with two known bisabolane-type sesquiterpenes, seven known flavonoids, and a known triterpenoid [126].

The aerial part of *Aster scaber* (known as edible Korean chamchwi; family Compositae) yielded two new monoterpene peroxide glycosides, (121) and (122), and other known compounds [127].

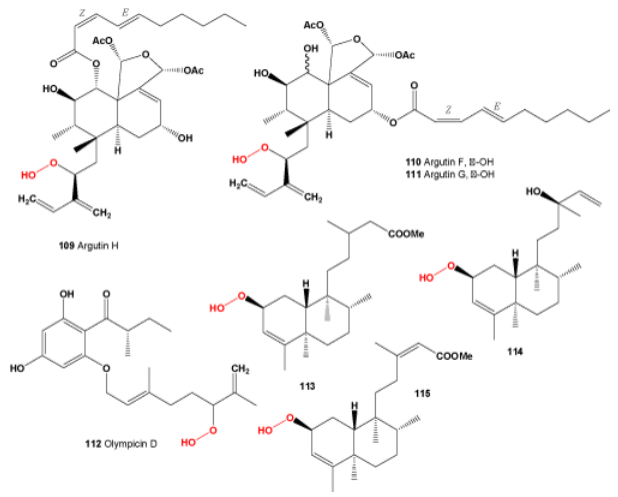

Figure 20: Bioactive plant hydroperoxides.

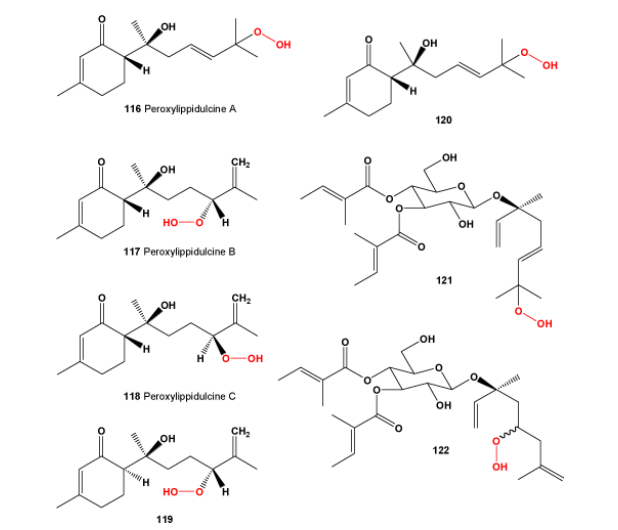

Figure 21: Bioactive plant terpene hydroperoxides.

Several dimeric sesquiterpene lactones (japonicones E-L), including a novel sesquiterpene dimer bearing a rare hydroperoxide group (japonicone E, 123) (Figure 22), were isolated from the aerial part of flowering plant *Inula japonica* (family Asteraceae). Compound (123) displayed strong inhibitory activity against LPS-induced NO production in RAW264.7 macrophages [77]. From the same species afforded additional related dimeric sesquiterpene, japonicone T (124) [78].

Cembrane-type diterpenoids with a trans-fused a-methylene-g-lactone, including two cembrane hydroperoxides 4-methylene-5β-hydroperoxy-ovatodiolide (125) and 4α-hydroperoxy-5-enovatodiolide (126) were isolated from a methanol extract of Indian Catmint *Anisomeles indica* (syn: *Nepeta indica*, *Anisomeles ovata*). Compound (126) exhibited cytotoxicity against a small panel of human cancer cell lines, and showed inhibitory effects on antiplatelet aggregation induced by thrombin [128].

Seven-membered vibsane-type diterpene hydroperoxides named 5-epi-vibsanin K (127), 18-O-methyl-5-epi-vibsanin K (128) as well as their corresponding C-5 epimers (129) and (130) 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 [129,130].

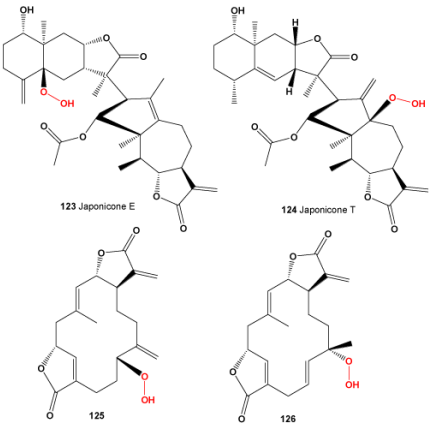

Figure 22: Plant hydroperoxides of terpene derivatives.

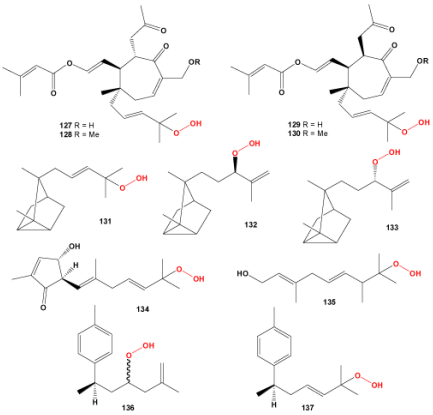

Figure 23: Plant hydroperoxides belonging to different classes of natural compounds.

Several santalane and isocampherenane sesquiterpenes, including three isomeric sesquiterpene hydroperoxides (131-133) 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 (−)-a-santalene by oxidation reactions [131,132].

Anti-HIV and cytotoxic activities of litseaverticillol A isolated from the twigs and leaves of shrub *Litsea 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 [133]. Synthesis of litseaverticillols B, E (134), I, and J as well as the structural reassignment of litseaverticillol E (134) 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 [134].

Compound (135) (Figure 23) was isolated from a multi-branched shrub *Heterothalamus alienus* (family Asteraceae; it *used* in Brazilian and Argentinean folk medicine) [135]. *Senecio* species are used for therapeutic purposes, including the treatment of fungal skin infections [136], antiseptic [137], and pneumonia [138]. The fresh aerial parts of *Senecio selloi* (family Asteraceae) contains two hydroperoxides (136 and 137), which were identified indirectly by isolation, identification and posterior photooxidation of α-curcumene, their precursor in the plant [139].

Four- and five-membered endoperoxides: Four-membered endoperoxides are rare in nature. A few members of this group have been discovered. Thus, a solubilised enzyme fraction of mycelium lyophilisate of *Pleurotus sapidus* convert of b-myrcene to furanoterpenoids throuth 1,4-endoperoxides, and compound (138) was isolated as intermediate [140].

Few four-membered endoperoxides (Figure 24) have only been found in nature. The unique neolignan mansoxetane (139), was obtained from the methanolic extract of the heartwood from *Mansonia gagei* (plant used in folk medicine in Thailand) [141], and sesquiterpenoid (140) was obtained from marine origin [142].

Two rare four-membered endoperoxides, named pheophytins, bidenphytins A (141) and B (141), with peroxide functionalities on ring E, were isolated from a flowering plant *Biden pilosa* var. *radiata*, a popular Taiwanese folk medicine. Possible biosynthetic pathway for 142 and 141 has been proposed [143].

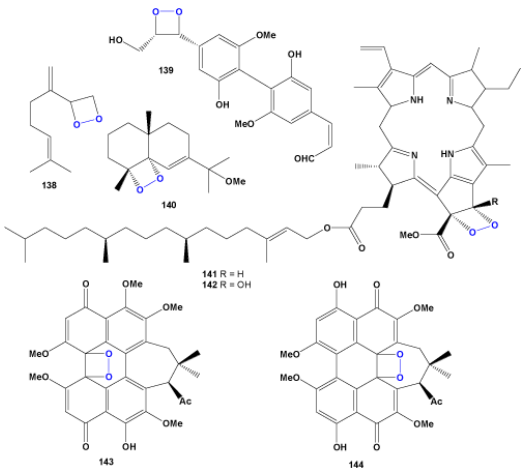

Figure 24: Rare plant four-membered endoperoxides.

Two four-membered cytotoxic peroxyhypocrellins (143 and 144) were obtained by the photooxidation of hypocrellin A [31]. Hypocrellin A has long been known as an excellent photosensitizer and has gained much attention in recent years because of its light-induced antitumor, antifungal and antiviral activities. It appears to exert photodynamic anticancer and antiviral activities through its abilities to generate reactive oxygen species and to inhibit protein kinase C activity, and it has also been shown to exert antimicrobial and antileishmanial activities *in vitro* [144].

A cyclic monoterpene peroxide (145) (Figure 25) with the irregular santolinyl framework was found from aerial parts of *Artemisia fragrans* [145]. A deciduous shrub *Artemisia maritima* is a species of wormwood known as sea wormwood and old woman produced the unusual five-membered ring peroxy hemiketal (146) [146]. Cytotoxic sesquiterpenes, (147-149) with moderate cytotoxicity were obtained from extracts of the aerial parts of *Artemisia abrotanum* [147]. The aerial parts of *Adenosma caeruleum* (family Plantaginaceae) of Vietnamese folk medicine contains cyclic peroxide (150) [148], and known metabolite cetylsaturejol (151) was detected in a small shrub *Satureja gilliesii* (family Lamiaceae) [149].

Nardostachys chinensis is an herbaceous member of the Valerian family, and the roots of this plant *contains* nardosinone (152) and kanshone B (153), and to possess weak antihepatotoxic activity [150]. Compound (152) was also a constituent of *Nardostuchjjs chinensis*, *N. juturnansi*, and Chinese spikenard oi1 [150,151].

Curcuma wenyujin (family Zingiberaceae) is a traditional medicinal herb in China (commonly known as Wen yujin), and compound wenjine (154) was found in extract of this plant [152,153].

A dimeric guaiane peroxide named vielanin C (155) was obtained from the leaves of *Xylopia vielana* (family Annonaceae), which it *used* in traditional medicine in Vietnam (Kamperdick et al., 2001). Eudesmane peroxide (156) to be present in extract from the roots of *Vladimiria souliei* (**pharmaceutical name:** *Radix Aucklandiae seu Vladimiriae*) [154].

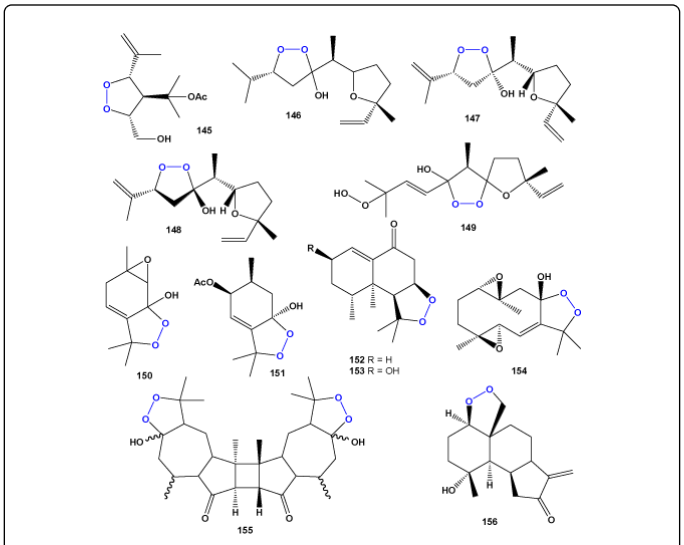

Figure 25: Plant five-membered endoperoxides.

Dimeric distansolides A (157) and B (**158**) were obtained from the flower heads of *Achillea distans* [155]. *Achillea* is a genus of over 100 flowering plants, and belonging to the family Asteraceae. A group of guaiane 6,10-endoperoxides (159-176) have been isolated from this genus: *A. asplenifolia*, *A. clavennae*, *A. collina*, *A. distans*, *A. ligustica*,

A. millefolium, *A. depressa*, *A. crithmifolia*, and *A. pseudoaleppica* [155-157]. Many of from these compounds showed cytotoxic, antibacterial and antifungal activities [157,158].

Sesquiterpene peroxide (177) has been found from the aerial parts of *Croton arboreous* [159]. *Artermisia filifolia* (known by common names including sand sagebrush, sand sage and sandhill sage) was the source for an interesting longibornan endoperoxide (178) [160]. Tehranolide (179) was a constituent of extract with the antimalarial activity of *Artemisia diffusa* [161] (Figure 26).

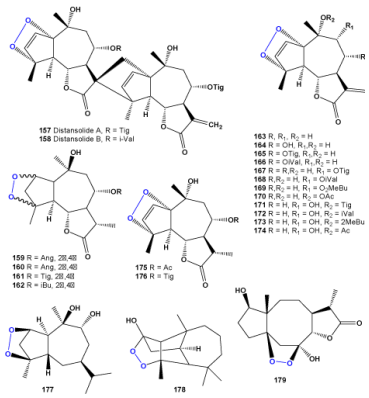

Figure 26: Plant five-membered terpene endoperoxides.

The seeds of the tree *Mammea americana* (family Calophyllaceae; commonly known as mammee, mammee apple, mamey, and mamey apple) contain two peroxy coumarin derivatives were isolated from the extract. The hydroperoxides (179) and (180) were optically active. The authors do not know whether the products result from metabolism within the seeds or are formed during isolation. Seeds of *M. americana* showed insecticidal activity (Structures showed in Figure 27).

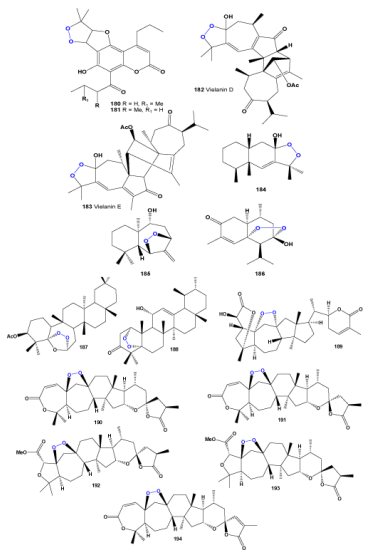

Figure 27: Five-membered endoperoxides from different plant species.

From the leaves of *Xylopia vielana* (Annonaceae, the custard apple family) two dimeric guaianes named vielanins D (182) and E (183) were isolated. These compounds consist of bridged ring systems formally representing the Diels-Alder products from the hypothetical guaiane-type monomers [162].

Three species of t*he genus Ligularia* (also known as leopard plant) perennial plants in the family Asteraceae: *L. kanaitzensis*, *L. subspicata*, and *L. veitchiana*, provided the eremophilane peroxide (184) [55,113,163].

A poisonous shrub *Illicium tsangii* (family Illiciaceae) from southern China used in traditional medicine for treating pain. Extract of this shrub contain allohimachalane peroxide (185) [131,132]. The aerial parts of the flowering plant *Ageratina adenophora* (syn. *Eupatorium adenophorum*) contain the sesquiterpene (186) [164]. Aceranol acetate (187), a 5,6-cleaved glutinane derivative, has been found in *Acer mandshuricum* (also known as Manchurian Maple) [165].

An ursane triterpenoid, 1α,5α-dioxy-11α-hydroxyurs-12-en-3-one (188) was isolated from the rhizome of *Vladimiria muliensis*. Isolated peroxide exhibited modest antimicrobial activity against *Escherichia coli*, *Candida albicans*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Bacillus cereus*, and *Staphylococcus aureus* [166]. Anticancer triterpenoid schinalactone A (189), an endoperoxide with an unusual contracted ring A, has been isolated from the roots and stems of a deciduous Climber *Schisandra sphenanthera*, it showed significant cytotoxicity against PANC-1 cell lines with a IC50 value of 5.9 μM [167]. Three triterpene peroxides, pseudolarolides Q (190), R (191), pseudolarolides T1 (192), T2 (193), and Q2 (194) were discovered from the leaves of *Pseudolarix kaempferi* (family Pinaceae) [168,169].

Six-membered endoperoxides: Ascaridole (195) and endoperoxy derivatives (196-198) (Figure 28) thereof were identified from essential oil of the fresh Chenopodium ambrosioides [112,170,171]. Ascaridole was first isolated in 1895 by a German pharmacist living in Brazil and it has been attributed with most of the vermifuge (worm-expelling) actions of the plant. In the early 1900's it was one of the major antihelmintics used to treat ascarids and hookworms in humans, cats, dogs, horses, and pigs [172-175]. Ascaridole (also known as ascarisin; 1,4-epidioxy-p-menth-2-ene) is a bicyclic monoterpene that has an unusual bridging peroxide functional group. Ascaridole has been documented with sedative and pain-relieving properties as well as antifungal effects [176]. Ascaridole was found to be a potent inhibitor in vitro development of Plasmodium falciparum [177], Trypanosoma cruzi [178], and Leishmania amazonensis [179]. Ascaridole also showed activity against different tumor cell lines in vitro (CCRF-CEM, HL60, MDA-MB-231). The findings are the first hint that ascaridole may be an interesting novel candidate drug for cancer treatment [180]. A few review articles devoted to pharmaceutical application of ascaridole have been published [4,181,182].

The the aquatic liverwort *Riella helicophylla* yielded two six-membered monoterpenes (199 and 200) [112]. The phytochemical investigation of the roots *Bombax anceps* (locally known as *Ngiu paa*; family Malvaceae) led to the isolation of dihydrobenzodioxine derivative, bombaxoin (201) [184]. Echinobithiophene A (202), a peroxide bithiophene with significant antimicrobial activity, was isolated from flowering plant *Echinops ritro* (family Asteraceae) [23]. Enzymatic extract from the leaves of *Piper crassinervium* (Piperaceae) afforded prenylated hydroquinone (203) [184].

An antitumor substance, the bisabolane sesquiterpenoid endoperoxide, 3,6-epidioxy-1,10-bisaboladiene (204), was isolated from the edible wild-plant, *Cacalia delphiniifolia* (Sanshoku). It showed cytotoxicity toward human chronic myelogenous leukemia K562 and human prostate carcinoma LNCaP cell lines with IC_{50} values of 9.1 μM and 23.4 μM, respectively. DNA fragmentation and condensation of chromatin, the hallmarks of apoptosis, appeared in K562 cells after an 18-h treatment with compound (204). The results indicate the importance of the endoperoxide structure within endoperodixe (204) to its anti-tumor activity *in vitro* [185]. This metabolite (204) has also been isolated from other plants including *Chamaemelum fuscatum* [186,187], *Encelia canescens* [188], *Eupatorium refescens*, *Heterothalamus alienus*, *Senecio selloi* [189,190], *H. psiadioides* [191], *Ligularia speciosa* [192], *Relhania genistifolia* [193] and *Smallanthus macvaughii* [194].

The buds of *Lonicera japonica* contained a cyclic peroxide named shuangkangsu (205) with significant antiviral activities [195]. A cembrane endoperoxide (206) was isolated from the flowers of Greek cultivated tobacco, *Nicotiana tabacum* [196].

Three compounds with a unique skeleton, i.e., apigenosylides A-C (207-209, respectively) (Figure 29) recovered from the EtOH extract of the leaves of *Machilus japonica* var. kusanoi. They possess an unprecedented skeleton comprising the adduct of a butenolide moiety and apigenin glycoside linked via a 1,2-dioxane moiety. Some of these compounds possess moderate inhibitory activity against α-glucosidase [197].

Steenkrotin B (210) has been isolated from an ethanol extract of the leaves of *Croton steenkampianus* (family Euphorbiaceae). Isolated compound showed cytotoxicity against african green monkey Vero cells by MTT assay, and antiplasmodial activity against chloroquine-susceptible *Plasmodium falciparum* D6, Dd2, w2, D10 [198]. This plant commonly known as Marsh Fever-berry and Tonga Croton, is a shrub or tree endemic to restricted areas of central and eastern parts of Africa. Various medicinal uses of the genus Croton are reported in countries all over the world, and many species are used to treat bleeding, bleeding gums, chest complaints, coughs, fever, indigestion, malaria, and rheumatism [199].

Unusual agent with anti-inflammatory activity named krameсyne (211), was isolated from a MeOH extract of *Krameria cystisoides* (Krameriaceae). This compound exhibited good anti-inflammatory activity in the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear edema (51.8% inhibition) and carrageenan-induced rat paw edema models at doses of 50 mg/kg. It also significantly reduced edema to 63.1% after 1.0 h and the effect was unchanged for 5h. Kramecyne (211) did not present acute toxicity, even at doses of 5 g/kg [200].

Several diterpenoids, abiesadines A-Y were isolated from the aerial parts of conifer *Abies georgei* (family Pinaceae), including three endoperoxides (212-214) (Figure 30). Some compounds showed the strongest effect against LPS-induced NO production in RAW264, anti-inflammatory activity, anticancer activity against LOVO cells [201]. Diterpenoid, caniojane (215), has found in the roots of flowering plant *Jatropha curcas* (family Euphorbiaceae) [202].

Taibaihenryiin T (216) was isolated from *Phlomis umbrosa* (sogdan is traditionally used as herbal medicines for healthy pregnancy and easy delivery in China, Japan, and Korea). The infrequency of the C-O-O-C group is manifested in this molecular configuration, and hydrogen bonding assembles the molecules into a three-dimensional networking structure in the crystal [203]. An unusual peroxy-multiflorane triterpene ester, (217), was isolated from the processed seeds of a flowering plant in the family Cucurbitaceae, *Trichosanthes kirilowii*. Compound (217) showed *in vitro* cytotoxicity against human tumor cell lines (Hela, HL-60, and MCF-7) and anti-inflammatory activity (LPS-induced B lymphocyte cells) [204].

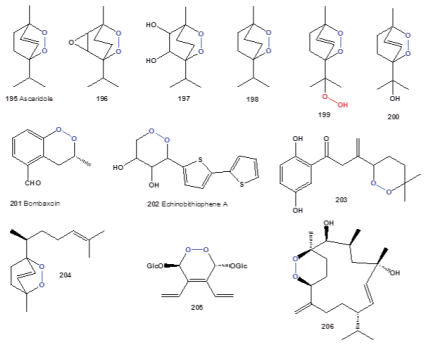

Figure 28: Six-membered endoperoxides from different plant species.

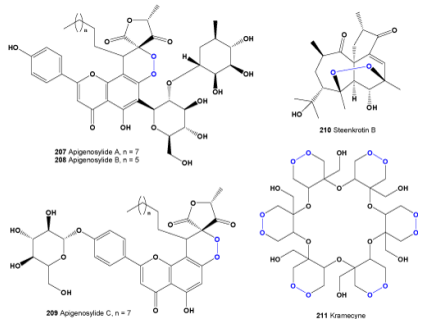

Figure 29: Six-membered endoperoxides from different plant species.

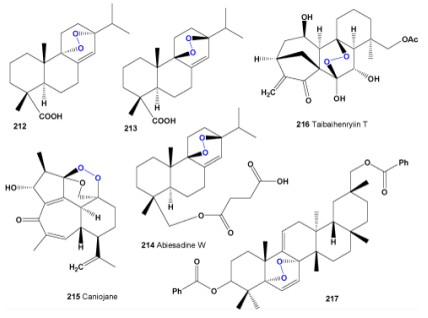

Figure 30: Plant six-membered terpene endoperoxides.

Seven-membered endoperoxides: Two prenylated benzophenone peroxide derivatives, peroxysampsones A (218) and B (219) (Figure 31), together with a known compound, plukenetione C, were isolated from the roots of the Chinese medicinal plant *Hypericum sampsonii*. These compounds are the unusual peroxides of polyprenylated

benzophenone derivatives, containing the unique caged moiety of 4,5-dioxatetracyclo (9.3.1.19,13.01,7) hexadecane-12,14,15-trione. Unusual peroxide (218) showed comparable activity with norfloxacin against a NorA overexpressing multidrug-resistant strain of *S. aureus* SA-1199B [205]. Sesquiterpene, 4-hydroxy-1,15-peroxy-eudesmane (220) was found in hexane extract from *Xylopia emarginata* fruits [206].

10,12-peroxycalamenene (221) was obtained from the dried tubers of *Cyperus rotundus* [207], and this compound has good *in vitro* antimalarial activity. Other antimalarial compound (222), is a constituent of cardamom, herb *Amomum krervanh* (family Zingiberaceae) [208]. *Artemisia annua* (known as sweet wormwood), afforded a rare seven-membered endoperoxide lactone arteannuin H (223) [209]. A labdane diterpene, coronarin B (224), and b-hydroxycoronarin B (225) were isolated from *Hedychium coronarium* (known also as white ginger lily) [210], and coronarin B has also been found in *Alpinia chinensis* [211].

Unusual metabolite (227) was discovered from *Xylopia emarginata* (family Annonaceae) and *Ecdysanthera rosea* (syn: *Urceola rosea*), respectively [206,212]. The eremophilane peroxide (228) was found in three species of the *Ligularia* genus (family Asteraceae): *L. subspicata*, *L. kanaitzensis*, and *L. veitchiana*, respectively [55,111,163].

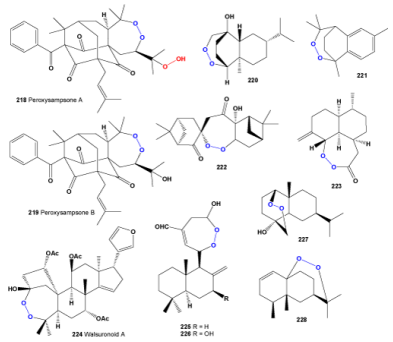

Figure 31: Plant seven-membered endoperoxides from plants.

Rare acyclic peroxides: Acyclic peroxides differ the other two types of peroxides: a) hydroperoxides and b) endoperoxides by the presence of the peroxy (-O-O-) linkage between the fragments of the same and/or other molecular structure. This bridge on the chemical structures marked in green. Several compounds were found in nature. Thus, acyclic peroxide oxanthromicin (26) (Figure 32) was isolated from an *Actinomadura* sp. fermentation broth [27,28], and two adxanthromycins A (27) and B (28) were found in the fermentation broth of *Streptomyces* sp. NA-148.

Dimethyl peroxide (229) was detected among the volatile components of *Basella rubra* (family Basellaceae) [213], and three other acyclic bis(1-hydroxyalkyl)peroxides (230–232) in the essential oil of Japanese citrus fruit, *Citrus iyo* (iyokan, also known as anadomikan) [214,215]. Extract of the Brazilian medicinal plant *Kielmeyera coriacea* (family Clusiaceae) afforded a δ-tocotrienol peroxy-dimer (234) [216], other peroxide dimer named bungein A (235) was found in the aerial parts of the medicinal plant *Clerodendrum bungei* (also known as Mexicali Rose, Mexican Hydrangea and/or Cashmere Bouque) [217]. Leucoperoxyterpene (236) with good antibacterial activity has been isolated from extract of aerial parts of the medicinal plant *Leucosceptrum canum* (family Laminaceae) [218].

Dimeric dihalenaquinolides A (237) and B (238), from marine origin, have a peroxide linkage between two meroterpenoid units [219]. Lactucin-8-O-p-methoxyphenyl acetate (239), a cytotoxic sesquiterpene lactone, has been detected in *Mulgedium tataricum* (family Compositae) [220].

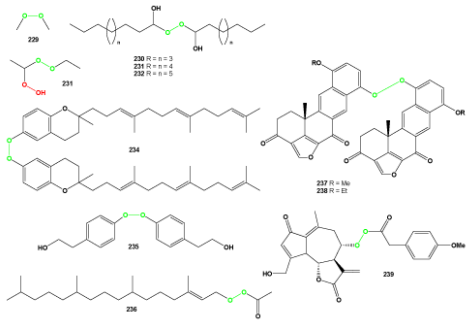

Figure 32: Rare seven-membered acyclic peroxides.

Conclusions

During the last 10-15 years, there has been an unprecedented growth in the chemistry of natural as well as synthetic peroxides. Currently, the rapid progress in chemistry of organic peroxides is to a large degree determined by their high biological activity. In medicinal chemistry of peroxides, particular emphasis is given to the design of compounds having activity against causative agents of malaria and human helminth infections. In medicinal chemistry of peroxides, for example, ascaridole and artemisinin a natural peroxides exhibiting high antimalarial activity, is the most important drug in use for approximately 30 years [1-5,8,9,221-225]. This review also emphasizes the role of peroxides from fungi, fungal endophytes, algae, plants, lichens, and bryophytes as an important source of leads for drug discovery.

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