Peroxy natural products
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This review covers the structures and biological activities of peroxy natural products from a wide variety of terrestrial fungi, higher plants, and marine organisms. Syntheses that confirm or revise structures or stereochemistries have also been included, and 406 references are cited.

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1 Introduction
This review, which is of the literature from 1998 to 2013, follows the pattern of its predecessors and is devoted to the new occurrence of peroxy compounds and described 639 naturally occurring peroxides from 406 articles. In the past more than 10 years, peroxy compounds have been isolated from a wide variety of terrestrial fungi, higher plants, and marine organisms, especially sponge species, many of which exhibited diverse biological properties such as anti-inflammatory, antimalarial, antimicrobial, cytotoxic, antitumor activities, and so on.

As a result of the potential for new drug discovery, peroxy compounds have attracted the attention of biologists and chemists throughout the world. So far, some reviews have dealt with the class of natural peroxides: “Peroxy natural products”, “Natural peroxy anticancer agents”, “Bioactive peroxy compounds as potential therapeutic agents”, and “Naturally occurring peroxy compounds with biological activities”. Other general reviews are: “Monoterpenoids”, “Sesquiterpenoids”, “Diterpenoids”, “Sesterterpenoids”, “Triterpenoids”, and “Marine natural products” all published in the journal Natural Product Reports covering from 1998 to 2011. References to other reviews are appropriately placed in the following sections.

In this review, we showed the structures of new peroxides, and previously-reported ones where there has been a structural revision or a newly-established stereochemistry. Previously-reported peroxides for which first syntheses or new bioactivities are described are referenced, but separate structures are generally not shown. Relevant data published in MEDLINE, Google Scholar, and SciFinder since 1998 have been gathered to formulate the following review.

2 Marine Metabolites
  2.1 1,2-Dioxane Carboxylates: Marine sponges, notably those from the genera Plakortis and Plakinastrella, continued to provide a source for six-membered ring cyclic peroxy compounds that incorporate a lactone ring. Plakortolides K–S (1–9) were isolated from the Australian sponge Plakinastrella clathrata. Detailed configurational investigation also revealed that the structure for previously reported plakortolide E should be...
revised to a non-peroxidic metabolite and the commonly assumed biosynthesis of the cyclic peroxide via Diels-Alder addition of singlet oxygen is incorrect. The first total synthesis of seco-plakortolide E also supported the structural revision of plakortolide E.

Continuing investigation of the same sponge, *P. clathrata*, afforded an additional set of 16 plakortolide metabolites 10–25. A Jamaican collection of *Plakinastrella onkodes* yielded two cyclic peroxides, plakortolide F 26 and plakortolide G 27. The absolute stereochemistry of plakortolide G was proposed from a combination of optical rotation and molecular modelling data. Plakortolide G exhibited potent inhibitory activity against the AIDS opportunistic parasitic infection *Toxoplasma gondii*. The trivial name plakortolide F was also given to a different peroxide 28, which was obtained from an unidentified species of *Plakinastrella* collected in the Seychelles. Two 1,2-dioxane peroxy lactones, plakortolides H and I 29 and 30, have been isolated from a Madagascar specimen of *Plakortis aff. simplex*, both of which were cytotoxic against a range of human tumour cell lines.

Several years later, the relative and absolute configurations of plakortolide I were revised on the basis of synthetic studies and reassignment of the NMR data, thereby establishing that the metabolite isolated was ent-plakortolide I 31. Whilst the trivial name plakortolide I has been proposed for an unnamed plakortolide metabolite 32 from the Philippine Sponge *Plakinastrella* sp., whose absolute stereochemistry was determined by application of Mosher’s method to a derivative. The authors also detail the unreliability of specific rotation measurements in the determination of absolute configuration within the plakortolide class of metabolites in the same paper. The first total synthesis of 32 has been achieved using a [2 + 4] photocycloaddition of a singlet oxygen to a diene and iodolactonization as key steps. A different species of *Plakortis*, *P. halichondrioides*, yielded additional peroxide-lactone named plakortolide J 33, the absolute stereostructure of which was determined by degradation reactions followed by application of Kishi’s method for the assignment of absolute configuration of alcohols. Synthetic efforts in construction the 1,2-dioxane ring of plakortolides have been described.

A further cyclic peroxide 34, with a terminal phenyl group but lacking the lactone, was isolated from *P. clathrata*. The ester represents further structural variation within the growing family of cyclic peroxycystino sugar metabolites.

The stolonoxides and stolonic acids are a family of natural aliphatic endoperoxides obtained from the samples of marine ascidians belonging to the genus *Stolonica*. Stolonoxide A 35, the first member of the series, was isolated as its methyl ester from the marine tunicate *Stolonica socialis*. A further investigation conducted on the same species yielded stolonoxides B–D 36–38, with strong cytotoxic activity against a panel of five tumor cell lines. The methyl ester derivatives of stolonoxides A and C have been identified as potent inhibitors of the mitochondrial respiratory. In addition, two new members of this structural class possessing a longer aliphatic chain, stolonic acids A and B 39 and 40, were isolated from an Indian Ocean Ascidian *Stolonica* species. Both compounds exhibited antiproliferative activity against selected human melanoma and ovarian tumor cell lines, with IC50...
values of approximately 0.05–0.1 μg/mL. Two new members of the stolonoxide family, stolonoxides E and F, were obtained from samples of the marine ascidian *S. socialis*. Both compounds displayed low micromolar cytotoxicity against a panel of human tumor cell lines.

The marine sponges of the genus *Plakortis* are also prolific producers of cyclic polyketide peroxides and structurally related compounds that exhibit a broad spectrum of biological properties. The bioactive cyclic peroxide plakortide Q has been isolated from marine sponge *P. zyggompha*, together with six cyclic peroxide analogues in their methyl ester forms. The relative stereochemistry of the 1,2-dioxane ring was established after interpretation of the coupling constant values and the NOESY data. Interestingly, a sample of the crude extract of the sponge left standing in methanol for one year yielded the methyl esters directly; this finding may go some way to accounting for the prevalence of methyl esters as reported metabolites of *Plakortis* species. The name plakortide Q was also proposed for a different peroxide, which was isolated from the Caribbean sponge *P. Simples*. In the same paper, the complete spectroscopic and stereostructural assignments of known 3-epi-plakortin has been reported. Three further cyclic peroxides, dihydroplakortin, plakortides I and J, were obtained from the same source, *P. Simplex*, by the same group, as well as providing the
absolute stereochemistries of known plakortin and plakortide H. The first synthesis of dihydroplakortin 51 has been achieved, featuring a one-pot three-step hydroperoxysilylation/cyclization reaction for the construction of the endoperoxide ring system. An insight into the mechanism of the antimalarial action of plakortin and dihydroplakortin, simple 1,2-dioxanes isolated from the sponge P. Simplex, has been reported.

The Australian marine sponge Plakortis sp. yielded two plakortide Q derivatives 54 and 55. Both were potent (nM) inhibitors of Trypanosoma brucei. Six cyclic peroxides 56–61 were isolated from an Okinawan Plakortis sp. and one of these, the peroxide 61, was shown to be cytotoxic. The antileishmanial peroxides 62 and 63 were reported from P. aff. angulospiculatus collected from Palau together with peroxide 64, which were inactive. Peroxides 56 and 64 have the same gross structure but the difference in optical rotations suggests that they have different stereochemistries. Fractionation of the sponge Plakortis sp. collected around the Amirantes Islands provided peroxides 63, 65 and 66. The relative and absolute stereochemistry of the cyclic peroxide 67, originally isolated from P. angulospiculatus, has been proposed by comparison to the optical rotation and NMR spectral data of synthesized diastereomers.

Two independent collections of an undescribed sponge Plakortis sp. from Discovery Bay, Jamaica, yielded four cyclic peroxides plakortides I–L 68–71, and two related compounds 72 and 73, respectively. Plakortide I represents the first report of a polyketide-derived cyclic peroxide with an α,β-unsaturated ketone moiety in the side chain and exhibits significant antimalarial activity against the W2 Clone of Plasmodium falciparum with an IC_{50} value of 570 ng/mL, whilst both 72 and 73 exhibited significant antimicrobial
activity against pathogenic bacteria and fungi with IC$_{50}$ values of 0.9–5.0 μg/mL and 0.7–8.0 μg/mL, respectively. The plakortides named I and J have been renamed plakortides M and N as the trivial names had been used previously for related metabolites isolated from P. Simplex. Unfortunately, the trivial names plakortides M and N were also proposed for another two compounds 74 and 75 from the Caribbean marine sponge P. Halichondrioides, which exhibited potent cytotoxicity to an array of human tumour cell lines. A Japanese specimen of Monotria japonica yielded the monotriajaponides B–D 76–78, which can lyse starfish oocytes without disruption of nuclear structure. Interestingly, the absolute stereochemistries of 76–78, as determined by reduction and a modified Mosher method, were opposite to those determined for the plakortides 74 and 75. Investigation of the bioactive crude extract from the sponge P. angulospiculatus from Brazil led to the isolation of the cyclic peroxide plakortenone 79. A sample of the Norwegian sponge P. simplex was found to contain two cyclic peroxides 80 and 81, of which 81 exhibited moderate in vitro activity against several solid human tumor cell lines with IC$_{50}$ values in the range 7–15 μg/mL. An Indonesian sponge P. nigra was the source of two isomeric cytotoxic trans epoxides, plakorstatins 1 (82) and 2 (83).

Three cytotoxic cyclic peroxides, ethyl plakortide Z 84, ethyl didehydroplakortide Z 85, which demonstrated selective activity in vitro against solid tumors but lacked activity in vivo, and methyl didehydroplakortide Z 86 were isolated from P. lita collected from Papua New Guinea. An Okinawan specimen of the same species provided two further cytotoxic endoperoxides, haterumadioxins A and B 87 and 88 with moderate cytotoxicity. Plakortide F, originally isolated from P. Halichondrioides, interfered with Ca$^{2+}$ homeostasis to mediate the antifungal activity.
A Jamaican collection of *P. Halichondrioides* afforded a peroxide acid 89 with moderate antifungal activity.48 A two-sponge complex comprising *P. halichondrioides* and *Xestospongia deweerdtae* (Bahamas) yielded one ω-phenyl polyketide peroxide named plakinic acid K 90. The absolute configurations of the isolated chiral centres were determined using liposomal circular dichroism and comparison with synthetic standards.49
Fractionation of the *P. onkodes* extract led to the isolation of the cytotoxic cyclic peroxide methyl capucinoate A 91 and the previously reported, but incompletely characterized, aromatic peroxide 92. Since *P. onkodes* was extracted in MeOH, the methyl esters 91 and 92 may be isolation artifacts. Four aromatic peroxides 93–96 were isolated from *Plakortis* sp. (Orote Peninsula, Guam), of which compounds 93 and 96 showed weak activity against *Staphylococcus aureus*, with MIC values of 128 and 64 μg/mL, respectively. Plakinic acid I 97 was obtained from *P. Halichondrioides*, and the absolute configuration determined from CD curves by degradation and liposomal ordering of naphthamide derivatives. Methylation of the crude extract of a *Sigmosceptrella* sp. from Southern Australia with diazomethane produced a mixture of products, from which nuapapuin methyl ester 98 and sigmosceptrellin D and E methyl esters 99 and 100 were isolated and identified. Their relative stereochemistries were assigned by established empirical rules and absolute stereochemistries by the advanced Mosher procedure. A plausible biosynthetic pathway has also been proposed that rationalizes key transformations in the biosynthesis of known norterpene cyclic peroxides and related norterpene ketones, dienes and sigmosceptrins.

Sponges of the genus *Diacarnus* are known to produce terpene peroxides and related metabolites. A norsesterterpene acid, named muqubilone 101, was isolated from the Red Sea sponge *D. Erythraeus*. It showed in vitro antiviral activity against herpes simplex type 1 (HSV-1). The same compound 101, named aikupikoxide A, was also isolated almost at the same time by the Scheuer group from the lipophilic extract of the Red Sea sponge *D. Erythraeus* along with three other cytotoxic cyclic norterpene peroxides, aikupikoxides B–D 102–104. The same source, *D. Erythraeus*, afforded another three cytotoxic norsesterterpenoid peroxides, tasnemoxides A–C 105–107.

Bioassay-guided isolation of *D. Levii* collected from Papua New Guinea led to the isolation of four norsesterterpene peroxides, diacarnoxides A–D 108–111, with diacarnoxides A and B displaying cytotoxic properties and increased activity under hypoxic conditions. Chemical investigation of the sponge *D. megaspinorhabdosa* provided a series of norterpene
derivatives, diacarperoxides A–G 112–118, of which, diacarperoxide D was cytotoxic. 59 Re-investigation of D. megaspinorhabdosa afforded one further norsesterpene cyclic peroxide, diacarperoxide S 119, which exhibited strong cytotoxic and antimicrobial activities. 60 Examination of D. bismarckensis (Sanaroa, Papua New Guinea) led to the isolation of two peroxiterpenes ent-(−)-muqubilone 120 and (+)-muqubilone B 121, active against Trypanosoma brucei (African sleeping sickness). 59,60 Specimens of D. cf. spinopoculum from the Solomon Islands and Papua New Guinea yielded a series of norsterpenes including four norsesterterpene peroxides, ent-muqubilin A 122, ent-epimuqubilin A 123, muqubilin B 124, and epimuqubilin B 125, and two norditerpene peroxides, nuapapuin B 126 and epimuapapuin B 127, all of which were evaluated for cytotoxicity using a soft agar assay system and the NCI’s 60 cell-line screening. Overall, the norsesterterpene peroxides were less selective as cytotoxins than norditerpene peroxide analogs. 65 The norsesterterpenoid peroxide, epi-muqubilin A 122, inhibited nitric oxide (NO) production in lipopolysaccharide (LPS)-activated murine macrophage RAW 264.7 cells, 55 and suppressed cyclooxygenase-2 via IKK/IκB/NF-κB pathways. 64,65 Esterification of carboxylic acid mixtures from the New Caledonian sponge D. levii resulted in the isolation of the benzyl esters of ent-muqubilin A 122 and deoxydiacarnoate B 128 and the methyl ester of diacarnoate B 129, all of which were screened for antimalarial activity. 66 Examination of the Taiwanese sponge Negombata cortica revealed a series of related peroxide terpenoids negombatoperoxides A–D 130–133. 67 Three norsesterterpene cyclic peroxides named trunculins G–I 134–136 were isolated as their methyl esters from an Australian Latrunculia sp., whose absolute stereochemistry about the cyclic peroxide terminus was established by application of the Horeau and Mosher procedures. 68
Investigation of a southern Australian sponge of the genus *Mycale* resulted in the isolation of one norsesterterpene mycaperoxide G methyl ester 137, which was obtained after treatment of the crude extract with diazomethane.\(^7\) The absolute stereochemistry previously assigned to mycaperoxide F methyl ester by application of the Horeau procedure has been revised by application of the Mosher procedure in the same paper. Bioassay-guided isolation of a Thai marine sponge *Mycale* sp. afforded a cytotoxic norsesterterpene mycaperoxide H 138. Its relative and absolute stereochemistries were established by standard methodology, including chemical interconversions.\(^8\) Synthetic efforts towards mycaperoxide B, originally isolated from a *Mycale* sp. from Thailand\(^9\), have been reported using a biomimetic approach.\(^2,3\)

### 2.2 1,2-Dioxolane Carboxylates

Although the majority of cyclic peroxides contain 1,2-dioxanes, while a growing number possess the more rare 1,2-dioxolane ring system. Bioassay-guided purification of a *Plakinastrella* species collected in the Seychelles led to the isolation of two moderately antifungal plakinic acid F 139 and epiplakinic acid F 140, containing a conjugated triene on the side chain.\(^1\) Examination of a Puerto Rican collection of *Plakortis halichondrioides* resulted in the isolation of two polyketide endoperoxides, epiplakinic acid F methyl ester 141 and epiplakinidioic acid 142 as well as providing the absolute configuration of known epiplakinic acid F.\(^16\) The antifungal plakorinsic acid 143 was isolated from a species of Jamaican *Plakortis*. The absolute configuration was determined by comparison of calculated and experimental optical rotations.\(^17\)

A Madagascar specimen of *P. aff. simplex* yielded one cyclic peroxide, andavadoic acid 144, which was cytotoxic against a range of human tumour cell lines.\(^18\) Two peroxide acids 145 and 146, isolated from *P. onkodes* collected in Florida, possessed moderate antifungal activity.\(^19\) The Palauan Sponge *P. nigra* provided two cyclic peroxides designated epiplakinic acids G and H 147 and 148. Isolated metabolites were found to inhibit the growth of HCT-116 cells.\(^20\) The first asymmetric synthesis of 1,2-dioxolane-3-acetic acids has been reported, and a further optimized strategy was applied to the synthesis of four stereoisomers of plakinic acid A,\(^21\) allowing a complete configurational assignment of plakinic acid A.\(^22\)

One ω-phenyl polyketide peroxide, plakinic acid L 149, was isolated from a two-sponge association of *P. halichondrioides* and *X. deweerdtae*.\(^23\) Synthesis of four possible diastereomers of plakortide E\(^24\) established the absolute configuration of plakortide E as shown.\(^25\) Plakinic acid J 150 was obtained from *P. Halichondrioides*, and the absolute configuration determined from CD curves by degradation and liposomal ordering of naphthamide derivatives.\(^26\) The Philippine sponge *Plakinastrella* sp. yielded two further cyclic peroxides 151 and 152.\(^27\)

### 2.3 Fatty Acid Derived Peroxy Ketals

Two acetylenic cycloperoxides named peroxycaranoic acids C and D (153 and 154) have been isolated as their methyl esters from the Indian sponge *Acarnus bicladotylota*,\(^28\) and the structurally related methyl peroxycaranoates A and B 155 and 156, have been found from the Red Sea marine sponge *A. cf. bergquistae*.\(^29\) The absolute stereochemistries of 153–155 were determined by the application of Mosher’s method. The syntheses of methyl peroxycaranoates A and D have been accomplished on the basis of chemoselective ozonolysis within a polyunsaturated framework and Pd-mediated cross-couplings of a functionalized 1,2-dioxane.\(^30\) The endoperoxylketal polyketides manadoperoxides A–D 157–160 with moderate antimalarial activity were isolated from the Indonesian sponge *Plakortis cfr. simplex* and their stereostructures were established by means of spectroscopic data and semisynthetic transformations.\(^31\)

Chemical investigation of the marine sponge *P. cfr. lita* afforded a library of endoperoxylketal polyketides named manadoperoxides E–K 161–167 and peroxylplakoric ester C 168, of which manadoperoxides F 162, H 164, I 165, and K 167 exhibited remarkable antitrypanosomal activity without cytotoxicity. The report have also demonstrated unambiguously that the endoperoxide group does not confer *per se* activity against Trypanosoma.\(^32\) The structures and absolute stereochemistries of known natural products chondrillin\(^33\) and its C-3 epimer, plakorin\(^34\) have been confirmed by syntheses of (+)– and (−)-chondrillin and (+)– and (−)-plakorin.\(^35\)

### 2.4 Diterpenes

One eucinellin-type diterpenoid astrogordin G 169 has been reisolated from a Chinese gorgonian *Astrogorgia* sp.,\(^36\) and the structurally related oxylitophynol 170 and klyximplexin D 171 have been obtained from the soft coral *Cladiella krempfi* and *Klyxum simplex*, respectively.\(^37,38\) From a biogenetical standpoint, oxylitophynol might derive from the formal photo-oxygenation of the corresponding Δ\(^2\) olefin. Another two substances of this type, briareellin K hydroperoxide 172 and briareellin D hydroperoxide 173, have been isolated.
from a Puerto Rican collection of *Briareum polyanthes*, and this study has also led to a revision of the structure of previously reported briarellin A to 174. The structure originally assigned to 11-acetoxy-4-deacetoxyasbestinin F has been revised to 175. Spectroscopic discrepancies observed for the enantioselectively synthesised structure originally proposed for alcyonin have led to the proposal that the correct structure of the natural product is the allylic peroxide 176.

Two dolabellane diterpenoids 177 and 178 with anti-protozoan activity have been obtained from a Colombian gorgonian coral of the genus *Eunicea*. New diterpenoid, 179 having a dolabellane skeleton, was isolated from the Okinawan soft coral of the genus *Clavularia*. This diterpenoid showed cytotoxic activity against several tumor cell lines. Other compounds of this type included calyculatine from *E. calyculata*, and (1R*,7R*)-7-hydroperoxydolabella-
Compound 181 showed strong cytotoxic activity against several cancer cell lines. One unusual pyran-ring containing cladiellane diterpene designated tritoniopsin B 182 was isolated from both the nudibranch Tritoniopsis elegans and its soft coral prey Cladiella kremp. Bioassay-guided fractionation of extracts from a Fijian red alga in the genus Calliophycus provided one new compound of the diterpene-benzoate class, bromophycoic acid C 183, which exhibited modest activities against methicillin-resistant Staphylococcus aureus and the human malaria parasite Plasmodium falciparum. Two xenophyllane peroxides gibberosins B and C 184 and 185 were isolated from a Taiwanese soft coral Sinularia gibberosa. Six further members of this family containing the unusual cyclic peroxyhemiketal moiety, sinugibberosides A–F 186–191, have been reported from the same species, S. Gibberosa. It is conceivable that the biogenesis of these compounds derives from intramolecular cyclisation of a hydroperoxide structurally related to gibberosin B. The Formosan soft coral Xenia umbellata collected in Taiwan,
China, contained a cytotoxic xenicane diterpenoid xeniolide G \( \text{G192} \). One meroditerpenoid, stypohydroperoxide \( \text{G193} \), was obtained from \textit{Stypopodium flabelliforme} (Long Island, Papua New Guinea).\(^{107}\)

One cytotoxic bromoditerpene \( \text{G194} \) and the related antibacterial bromoditerpene 2\(S\)-hydroperoxy-12\(R\)-hydroxy-isobromosphaerol \( \text{G195} \) were successively isolated from the same collection of \textit{Sphaerococcus coronopifolius} by the same group. The structure of the previously reported 12\(S\)-hydroxy-bromosphaerodiol\(^{108}\) and 2\(S\),12\(S\)-dihydroxyisobromosphaerol\(^{109}\) were revised to \( \text{G196} \) and \( \text{G197} \), respectively. The absolute stereochemistry of \( \text{G194} \) was established by X-ray crystallographic analyses.\(^{110,111}\)
Chemical investigation on the gorgonian coral *Briareum* sp. yielded a hydroperoxybriarane diterpene named briarenolide B 198 with a rare 9-ketobriarane moiety. The same group afforded a further related briarenolide D 199 from a cultured specimen of the same organism. Four diterpene compounds...
200–203 representing a new skeletal type, the dactylomelanes, have been found from specimens of Laurencia sp.114

A large number of highly functionalized cembranoid diterpenes and related metabolites have been isolated and identified from marine soft corals, especially from the genera Lobophytm, Sarceophyton, and Sinularia. A hydroperoxy-substituted cembranoid diterpene, 2-hydroperoxysarcophine 204, was isolated from South-China-Sea soft coral L. crassum. It remains unclear whether 204 is a true natural product or an artifact.115 One further cembranoid, crassumolide E 205, was found from the same species.116 A Kenting (Taiwan) collection of Sinularia flexibilis contained the cembranoid hydroperoxide flexilarin C 206.117 The same group provided two further structurally-related \( \varepsilon \)-lactones similarterpenes A 207 and B 208 from the same species.118 The Taiwanese soft coral S. manaarensis contained four cembrane-type diterpenoids, manaarenolides A 209 and B 210 and manaarenolides E 211 and F 212, which were discovered for the first time as the hydroperoxycembranolides possessing a \( \delta \)-lactone ring.119 Four \( \gamma \)-cembranolide-type diterpenes, uprolides H–J 213–214 and L 215 and M 216, were reported from Eunicea pinta collected from San Andrés Island, Colombia. This study also led to the revision of the structures for nine previously reported uprolide B, uprolide B acetate, 8-epi-uprolide B, uprolide C acetate, 8-epi-uprolide B acetate,120 12,13-bis-epiuprolide B, 12,13-bisepiuprolide B acetate, uproeunicin, and uprolide C121 to 217–225, respectively.122 Another compound of the type...
226 was isolated from the soft coral *Sarcophyton crassocaulen* collected from the Xisha Islands in South China Sea. It exhibited strong cytotoxicity against the P388 cell line with an IC$_{50}$ value of 0.1 μg/mL. The same source, *S. crassocaulen*, provided three further cembranoid sarcocraсcolides F 227, G 228, and J 229, all of which inhibited LPS-induced up-regulation of the pro-inflammatory protein iNOS. A chemical investigation of another species of the same genus, *S. Glaucoma*, has led to the isolation of two peroxide diterpenes 230 and 231, the absolute configuration of which were confirmed by X-ray diffraction and circular dichroism (CD) analyses. Compound 231 was found to be promising inhibitors of cytochrome P$_{450}$ 1A activity as well as inducers of GST and QR activity in vitro assays.

A decalin-type bicyclic diterpenoid, lemnaloside C 232, has been obtained from an extract of the marine soft coral *Lemnalia* sp. The Japanese marine sponge *Epipolaisis* sp. afforded a novel diterpene peroxypolasol 233. The Formosan soft coral *Nephthea pacifica* contained four prenyl bicyclogermacrane diterpenoids, pacificins C 234, E 235, G 236, and H 237, of which, 234 and 237 exhibited cytotoxicity against P388 cells with ED$_{50}$ of 1.44 and 2.01 μg/mL, respectively.

2.5 Other Marine Metabolites: The Hainan Sponge *Dysidea septosa* contained a new sesquiterpene lingshiaperoxide 238. Three isothiocyanate sesquiterpenes axinisothiocyanates H 239 and I 240, axinisothiocyanate N 241, and aristolane derivative axinisone C 242 have been obtained from a sponge of the genus *Axinyssa* collected in the Gulf of California by the same authors. Axinisothiocyanate N were mildly cytotoxic.

Hydroperoxides have rarely been found in algae: two examples, dictyohydroperoxide 243 and hydroperoxyacetoxycenulide 244, were isolated from *Dictyota dichotoma* (Troitsa Bay, Sea of Japan, Russia). A aromandendrane sesquiterpenoid 245 was isolated from the Formosan soft coral *Clavalaria inflata*. Chemical investigations of the soft coral *Nephtea erecta* have afforded three new sesquiterpenoids 246–248, of which, 247 and 248 exhibited significant cytotoxicity against P388 and HT-29. The Formosan soft coral *Nephtea erecta* provided the sesquiterpenoid 249. Five sesquiterpene peroxides sinularioperoxides 250–254 have been isolated from a Formosan soft coral of the genus *Sinularia* by the same group.

An unusual 1,2-dioxolane-3-ol-containing sesquiterpene,
diososarcoguaiacol 255, was reported from an Egyptian (Red Sea) collection of *Sarcophyton glaucum*. A *Dysidea* sp. from the Great Barrier Reef contained a cytotoxic sesquiterpene 256, the structure of which was determined by single crystal X-ray analysis. Bioassay-guided fractionation of the Okinawan marine sponge *Dysidea chlorea* afforded two tricyclic spiro-sesquiterpenes, haterumadysins C and D 257 and 258, both of which may be isolation artifacts. One cuparene-derived sesquiterpene, laureperoxide 259, has been reported from the red alga *Laurencia okamurai*. The guaiane derivative peroxygibberol 260 has been obtained from the Formosan soft coral, *Simularia gibberosa*, which was found to exhibit moderate cytotoxicity toward a human liver carcinoma cell line. The sipholane-type triterpenoids, sipholenol M 261, siphonellinol E 262, and siphonellinol hydroperoxide 263, were isolated from the red sea sponge *Callispongia (Siphonochalina) siphonella*. Although there are several documented natural plant-derived triterpene hydroperoxides in the literature, it is also plausible that these three compounds are artifactual oxidation by products generated during the extraction and isolation process. *Bruguiera gymnorrhiza* yielded a dammarane-skeletone d triterpene bruguierin C 264 that activated antioxidant response element with micromolar potency.
A Mediterranean collection of *Placida dendritica* afforded an unprecedented hydroperoxide 265. Whether the hydroperoxide is an artifact of isolation, or a true natural product is unclear. One halogenated nonterpenoid C₁₅-acetogenin, laurendecumenyne A 266, has been reported from the Marine Red Alga *Laurencia decumbens*. Dihalenaquinolides A 267 and B 268, from the Taiwanese marine sponge *Petrosia elastica*, have an unusual peroxide linkage between two meroterpenoid units. Bioassay-guided fractionation of the marine cyanobacterium *Lyngbya* sp. led to the isolation of biselyngbyasides C 269 and D 270, whose stereochemistries were established based on NOESY spectra and CD data.

Two prenylated indole diketopiperazine alkaloids, spirotryprostatin E 271 and 13-oxoverruculogen 272, have been obtained from the fermentation of *Aspergillus fumigatus* from a holothurian, *Stichopus japonicus* (Lingshan Is., Qingdao, China). The antimarial gracilioether A 273, from the sponge *Agelas gracilis* (Oshima-Shinsone, Japan), are of mixed acetate/butanoate origin. The sponge *Plakinastrella mamillaris* was a new source for gracilioether A 273. The existence of endoperoxide ring is important for the antimalarial activity.

A collection of the sacoglossan *Placobranchus ocellatus* from the Philippines provided three propionate-derived metabolites, tridachiapyrone J 275, and tridachial hydropyrones B 276 and C 277, all of which are probably artifacts from oxidation during storage or workup. Several years later, tridachial hydropyrones B and C were proved to be the same compound characterized as 278. The same species, *P. ocellatus*, provided the possibly artefactual peroxy derivative 279, whose relative configuration was confirmed at the same year. A Panamanian collection of the sacoglossan mollusc *Elysia diomedea* yielded the endoperoxide 280, structurally closely related to 279. The observation of rearrangement of 280 with triethylamine to yield the known vicinal diexpoxide elysiapyrone A 158 prompted speculation of the biosynthetic intermediate of 280, likely to be in turn derived from a putative polypropionate alkenyl chain-containing precursor reacting with singlet oxygen.

3 Terrestrial Sources

3.1 Monoterpenoids: One *p*-menthane hydroperoxide, (1R,4S)-1-hydroperoxide-3-menth-2-en-8-ol-acetate 281 with strong trypanocidal activity, was isolated from the leaves of *Laurus nobilis*. The same group afforded four further monoterpenes hydroperoxides 282-285 with trypanocidal activity from *Chenopodium ambrosioides*. These hydroperox-
ides are likely formed through the singlet-oxygen oxidation of limonene, and the hydroperoxy group is essential for their trypanocidal activities.\textsuperscript{160} The liverwort \textit{Riella helicophylla} yielded six new monoterpenes \textsuperscript{286–291}.\textsuperscript{161} The aerial part of \textit{Aster scaber} afforded two monoterpene peroxide glycosides \textsuperscript{291–293}.\textsuperscript{162} A cyclic monoterpene peroxide \textsuperscript{294} with the irregular santolinyl framework was found from aerial parts of \textit{Artemisia fragrans}.\textsuperscript{163} The complete stereostructure of \textsuperscript{295} has been established by application of the modified Mosher method.\textsuperscript{164} Catharoseumine \textsuperscript{296}, a monoterpenoid indole alkaloid possessing a unique peroxy bridge moiety, was isolated from the whole plants of \textit{Catharanthus roseus}. Its absolute configuration was determined by ECD and chemical methods. Catharoseumine exhibited cytotoxicity against HL-60 cell line with IC\textsubscript{50} value of 6.28 \(\mu\)M and potential inhibition against \textit{Plasmodium falciparum} falcipain 2 (IC\textsubscript{50} = 4.06 \(\mu\)M). A plausible biogenetic pathway of catharoseumine was also proposed.\textsuperscript{165}

### 3.2 Sesquiterpenes

#### 3.2.1 Guaianes: \textsuperscript{309} Three highly oxygenated guaianolides \textsuperscript{297–299} were isolated from the aerial parts of \textit{Ajania
fraticulosa. Compound 299 was inhibitory to the growth of Candida albicans with MICs being 20 μg/mL. The aerial parts of Achillea setacea afforded a guaianolide 300 containing an endoperoxide ring. Two guaianolides, anthemolide B 301 and 8-O-angeloyl-9-O-acetylanthemolide B 302, were identified from the aerial parts of the flowering plant Anthemis cretica. A cytotoxic sesquiterpene lactone, lactcin-8-O-p-methoxyphenyl acetate 303, has been isolated from nature. The structure of 1

Chemical examinations of the roots of Nardostachys chinensis afforded two antimalarial guaiane endoperoxides, nardoperoxides 305 and 306, whose absolute stereochemistries were determined by CD spectra. The endoperoxide moiety of the molecules was assumed to relate to the antimalarial activity. A subsequent report described another four related endoperoxides nardoguaianones A 307–310 from the same plant. Three hydroperoxides 311–313 with trypanocidal activity have been isolated from Pogostemon cablin whilst the sesquiterpene peroxyacid 314 has been found from the aerial parts of Croton arboresus.

3.2.2 Eudesmanes: The aerial parts of Montanoa hibiscifolia afforded three eudesmanolides 315–317 with a rare endoperoxide structural element. The novel eudesmanolide 318 has been isolated from Atractylodes macrocephala. The aerial parts of Aster spathulifolius was the source for two cytotoxic sesquiterpene hydroperoxides, 7α-hydroperoxy-3,11-eudesmidane 319 and 7β-hydroperoxy-eudesma-11-en-4-ol 320. The sesquiterpene schisan-3-one A 321 was identified from the species Schisandra sphenanthera. A eudesmane derivative hydroperoxy-gynuradiene 322 has been obtained from the root of Gynura bicolor. Another two compounds of this type 323 and 324 were discovered from Xylopia emarginata and Ecdysanthera rosea, respectively.

Two novel eudesmane-type sesquiterpene peroxyacids, kandenols C 325 and D 326, have been reported from Streptomyces sp. derived from the mangrove plant Kandelia candei. The aerial parts of Inula japonica contained two eudesmane sesquiterpenoids 327 and 328. Compound 328 was confirmed by means of single-crystal X-ray diffraction analysis. One eudesmane derivative 329 has been isolated from the liverworts Chiloscyphus polyanthus. Other eudesmane peroxyacids included 1β,14-peroxy-4α-hydroxy-5αH,7αH,6β-H-eudesmin-11(13)-ene,12-olide 330 from the roots of Vladimiria souliei. 3α-dehydroxy-3α-hydroperoxy-cyclopelotriol 331 from Achillea clypeolata, and 5α-hydroperoxy-eudesma-4(15),11-diene 332 from Artemisia annua.

3.2.3 Bisabolanes and Germacranees: Four bisabolane-type sesquiterpenes, peroxylippidulcines A–C 333–335 and
peroxyepilippidulcine B 336, have been obtained from the aerial parts of *Lippia dulcis*. The relative configurations of 334 and 336 were confirmed by X-ray crystallographic analysis data.\(^{191}\) The aerial parts of *Carthamus lanatus* afforded two oxygenated bisabolane fucosides 337 and 338.\(^{192}\) Another species of the genus, *C. glaucus*, contained two bisabolane fucopyranosides 339 and 340.\(^{193}\) Another bisabolene derivative 341 was found from the aerial parts of *Achillea clavennae*.\(^{194}\)

A germacrane peroxide 342 was identified as a component of *mulgedium tataricum*.\(^{170}\) Chemical investigation of *Santolina insularis* afforded two germacrane sesquiterpene peroxides 343 and 344, which might derive from the formal photo-oxygenation of the corresponding \(\Delta^\alpha\) olefin, a reaction well preceded in medium-sized olefins.

3.2.4 Sesquiterpene Dimers: A dimeric sesquiterpene lactone japonicone E 345 bearing a rare hydroperoxide group was obtained from the aerial parts of *Inula japonica*, which displayed strong inhibitory activity against LPS-induced NO production in RAW264.7 macrophages.\(^{196}\) Further investigations of the same species afforded additional related dimeric sesquiterpene, japonicone T 346.\(^{197}\) The leaves of *Xylopia vielana* contained a dimeric guaiane peroxide named vielanin C 347 with a central cyclobutane ring that are generated from two equal guaiane moieties by \([2 + 2]\) cycloaddition.\(^{198}\) Two further related vielanins D 348 and E 349 were isolated from the same plant as epimeric mixtures. Both compounds consist of bridged ring systems formally representing the Diels-Alder products from the hypothetical guaiane-type monomers.\(^{199}\) Spicachlorantins C–F 350–353, new lindenane sesquiterpene dimers possessing a hydroperoxy group, were isolated from the roots of *Chloranthus spicatus*, whose absolute stereostructures were established by CD spectroscopic analyses. These compounds were considered to be biogenetic precursors of the corresponding hydroxyl derivatives of dimeric lindenane sesquiterpenoids distributed in *Chloranthus* plants.\(^{200}\) Another species of the genus, *C. Japonicus*, contained one more dimeric sesquiterpene peroxide 354, structurally related to 350–353.\(^{201}\)
3.2.5 Other Sesquiterpenes: The structures of cytosporolides A–C \(\text{355–357}\) have been revised on the basis of synthetic studies and reinterpretation of the NMR data. Cytosporolide A, which was originally assigned the strained nine-membered peroxylactone structure, has been revised to \(\text{358}\), which is probably biogenetically formed by a hetero-Diels-Alder type cyclization.
The novel norsesquiterpene peroxides steperoxides A–D 359–362 have been obtained from the mushroom Steccherinum ochraceum, while another nor-chamigrane merulin A, and the chamigranes merulins B–D 363–365, have been found in an extract of the culture broth of a Thai mangrove-derived fungus. We have observed that steperoxide B and merulin A have the same structure 360. Among these isolated metabolites, merulin C exhibited potent antiangiogenic activity. Another four compounds of this type, talaperoxides A–D 366–369, have been obtained from Talaromyces flavus. Talaperoxides B and D were moderately cytotoxic to several human tumour cell lines. The structures of 359, 360, 366 and 367 were further confirmed by X-ray crystallographic analysis, and the absolute configurations of the latter three compounds were also determined using copper radiation.

Five peroxycuparene-type sesquiterpenoids 370–374 were identified from the Japanese liverwort Jungermannia infusca. The stereostructure of 370 was confirmed by X-ray crystallographic analysis. An inseparable diastereomeric mixture acetylmajapolene A 375 in the part of the peroxide with antibacterial activity have been found in an extract of an undescribed Malaysian species of the Laurencia genus, whose absolute configurations have been unambiguously determined as (1R,4R,7S,10S) and (1S,4S,7S,10S), respectively, by vibrational circular dichroism (VCD).

Two novel muurolane sesquiterpene peroxides, 1,4-peroxy-muurol-5-ene 376 and 1,4-peroxy-5-hydroxy-muurol-6-ene 377 have been obtained from Illicium tsangii. The absolute stereochemistry of 376 was confirmed by X-ray crystallography. A peroxymuurolane-type sesquiterpenoid 378 was isolated from the Belguem liverwort Scapania undulata. The essential oil of the liverwort Plagiochila asplenoides contained one oxygenated sesquiterpene (+)-muurolan-4,7-peroxide 379. The NMR data of the sesquiterpene peroxide 380 are also reported for the first time in the same paper. The aerial parts of the invasive plant Eupatorium adenophorum contain the new sesquiterpene 381. Dihydroartemisinic acid hydroperoxide 382 was isolated for the first time as a natural product from the plant Artemisia annua. The compound is a probable precursor of artemisinin under nonenzymatic conditions. The same plant, A. annua, afforded a rare seven-membered endoperoxide lactone arteannuin H 383, a biomimetic synthesis of which has confirmed biogenetic speculations regarding its formation from a secondary allylic hydroperoxide. The structure of 384, isolated from the leaves of Eupatorium adenophorum, was determined by single-crystal X-ray crystallography.

A phytochemical study of Robinsonioecio gerberifolius afforded a eremophilane derivative 385, whose absolute configuration was established from CD analysis. Three species of the Ligularia genus, L. subspicata, L. Kanaizensis, and L. Veitchiana, provided the eremophilane peroxides 386, 387, and 388, respectively. Another compound of this type 389 was isolated from Cacalia tangutica.

The aerial parts of Anthenis arvensis contained two irregular linear sesquiterpene lactones 390 and 391, both of which were re-isolated from the same plant by another group of researchers. A different species of Anthenis, A. cotula, afforded additional related peroxide, 5-hydroperoxy-6,13-dehydro-5,6-dihydroanthecotoluolide 392.

Three isomeric sesquiterpene hydroperoxides 393–395 were isolated from Illicium tsangii. These compounds appear to be derived from the one-type addition of molecular oxygen to the known compound a-santalene. A bioassay-guided fractionation of extract from Scleria straitnarius led to the
isolation of okundoperoxide 396, a compound with antiplasmodial activity. 231

The aerial parts of Xanthium strumarium contained one xanthane-type sesquiterpenoid, 4β,5β-epoxyxanthatin-1α,4α-endoperoxide 397. 232 One allohimachalane peroxide has been obtained from Illicium tsangii. 233 The extract of the aerial parts of Artemisia diffusa contains tehranolide 399, a new type of sesquiterpene lactones with an endoperoxide group. 234 Successful biomimetic syntheses of the litseaverticillol family of sesquiterpenes have been achieved, using singlet oxygen chemistry. 235 In this work, the structure of the previously reported litseaverticillol E 236 has been revised to 400.

Artemisinin, the well-known antimalarial agent, has been the focus of continuing study. Its antimalarial activity, structural modification, structure-activity relationships, mode of actions, and use in therapy have been well reviewed. 237–240

3.3 Diterpenes: A dolabellane diterpene derivative 401 with the naturally rare peroxy function was identified as a component of the aerial parts of Cleome droserifolia; 241 and additional related peroxide 402 was found from Aglaia odorata. 242 Jatropha integerrima provided a rhamnololane endoperoxide 2-epicaniojane 403, whose structure was confirmed by X-ray diffraction analysis. 243

A clerodane peroxide, 15(16)-peroxy-3,13-clerodadien-18-oic acid 404, was isolated from the Taiwanese liverwort Schistochila acuminata, 244 and the structurally related 2β-hydroperoxykolavelool 405 was reported from Aristolochia chamissonis. 245 The plant Casearia arguta afforded further members of the series, argutins F–H 406–408.

The aerial parts of Aster oharai contained two labdane peroxides 409 and 410, of which compound 409 showed moderate cytotoxicity against several human tumor cell lines with ED_{50} values ranging from 1.1 to 7.7 μg/mL. 247 A different species of Aster, A. spathulifolius, provided further related 7α-hydroperoxymanool 411 that showed moderate cytotoxicity against human cancer cells. 179 Other compounds of this type included (8S)-hydroperoxy-(13S)-hydroxy-9(11),14-labdadiene 412 from Jungermannia infuscata, 248 ent-12,15-dioxo-3,4-seco-4,8,13-labdatrien-3-oic acid 413 and ent-12,15-dioxo-8,13-labdadien-3α-ol 414 from Croton stipuliformis, 249 and 8α-hydroxy-13-hydroperoxylabd-14,17-dien-19,16:23,6α-diolide 415 from Salvia sahendica. 250 The absolute stereochemistry of compound 414 was determined by application of Mosher’s method.
The leaves of *Viburnum awabuki* afforded two vibsane hydroperoxides vibsanin K 416 and 18-O-methylvibsanin K 417 as well as their corresponding C-5 epimers 418 and 419, of which vibsanin K exhibited significant cytotoxicity against human gastric (NUGC) and oral epidermoid (HONE-1) tumor cells at a concentration of 50 μg/mL. An unusual macrocyclic endoperoxide structure was assigned to neovibsanin C 420 that was obtained from *Viburnum aurabuki*. Two cytotoxic diterpenes, dysokusones B 421 and C 422, were isolated from the stem of *Dysoxylum kuskusense*. A rare open chain peroxide designated
leucoperoxyterpene 423 with good antibacterial activity has been isolated from aerial parts of the medicinal plant *Leucosceptrum canum*.\(^{255}\)

Jungermatrobrunin A 424, which was obtained from the liverwort *Jungermannia atrobrunnea*, has an unusual rearrangedent-kaurene skeleton with a peroxide bridge. Its relative configuration was further supported by a single-crystal X-ray crystallographic analysis.\(^{256}\)

A phytochemical investigation on the stems of *Annona squamosa* led to the isolation of additional two *ent*-Kaurane hydroperoxides, annosquamosins F 425 and G 426.\(^{257}\)

The leaves of *Croton steenkampianus* provided a novel diterpenoid steenkrotin B 427, which possess a novel carbon skeleton that may be derived from the daphnanetype by an 8(9→10)-abeo rearrangement.\(^{258}\) A rare 3,4,5-seco-elestanthane hydroperoxide designated as trigonochinene C 428 with antimicrobial activity was isolated from the aerial parts of *Trigonostemon chinensis*.\(^{259}\)

Nine jatrophane hydroperoxides, amygdaloidins C 429 and E–L 430–437, have been isolated from the wood spurge, *Euphorbia amygdaloides*.\(^{260}\) A methanol extract of *Anisomeles indica* afforded two cembrane hydroperoxides 4-methylene-5β-hydroperoxyovatodiolide 438 and 4α-Hydroperoxy-5-enovatodiolide 439, of which 439 showed inhibitory effects on antiplatelet aggregation induced by thrombin.\(^{261}\)

Two abietane endoperoxides 440 and 441 were isolated as the corresponding acetate derivatives from the cones of *Cedrus atlantica*.\(^{262}\) The aerial parts of *Illicium angustisepalum* contained four more abietane diterpenes, angustanoic acids B–D 442–444 and I 445.\(^{263}\) Investigation of the leaves and twigs of *Callicarpa longissima* resulted in the isolation of a 3,4-seco-abietane peroxide named callilongisins A 446 with significant anti-inflammatory effect, whose structure was further confirmed by X-ray crystallographic analysis.\(^{264}\)

Three diterpenic acids 447–449 were isolated as their methyl ester derivatives from the leaves of *Juniperus thurifera* and...
Juniperus phoenicea. Further members of the type included triptotins A 450 and B 451 from Tripterygium wilfordii, 6-oxo-12-peroxyabieta-8,11,13-triene 452 from Salvia multiflora, and glutinosin C 453 from Isodon glutinosus. The structures of triptotin A and glutinosin C were confirmed by single crystal X-ray analysis. Phytochemical investigation of the above-ground parts of Siegesbeckia pubescens yielded one ent-pimarane diterpenoid 454.

3.4 Triterpenes: A taraxastane-type triterpene, 3β-acetoxy-19ɑ-hydroperoxy-20-taraxastene 455, has been isolated from the aerial roots of Ficus microcarpa. Reinvestigation of the aerial root extract afforded five ursene derivatives 456–460. The structure of 460 was confirmed by X-ray crystallography. Another compound of this type 461 was obtained from Arnica montana. The rhizome of Vladimíria multilis was provided one antimicrobial ursane triterpenoid 1α,5a-dioxy-11β-hydroxyurs-12-en-3-one 462. Other ursene triterpenoids were including 3β,28-dihydroxy-11β-hydroperoxy-12-ursene 463 from Tolpis proustii and speciosaperoxide 464 from Chaenomeles speciosa. Other ursene triterpenoids were 3β,28-dihydroxy-11β-hydroperoxy-12-ursene 463 from Tolpis proustii and speciosaperoxide 464 from Chaenomeles speciosa.

Ginsenoside Sg2 467 has been isolated from black ginseng. A pair of allylic hydroperoxides, ginsenoside-Rh2 and ginsenoside-Rh5, have been reported from the leaves and flower buds of Panax ginseng, respectively. Ginsenosides Sg2 and displayed potent scavenging activity with the inhibition value of 64% at 10 μM. The same species contained six dammarane-type triterpene diglycosides, floralginsenosides A–F 470–475, five dammarane triterpene triglycosides, floralginsenosides G–K 476–480, and a dammarane triterpene obligoglycoside, ginsenoside SF 481–483.

Six dammarane triterpenes, named proboscidersol D–I 482–487, have been found in Prosoceidea louisiana. The stem bark of Rhus javanica contained a dammarane triterpene designated as isofouquierone peroxide 488. Ginsenosides I and II from Panax ginseng have new genins 489 and 490. The fruits of Ceriopis tagal was the source for a dammarane triterpene cereotagaloperoxide 491. Aglaia brevifolia F 492 was identified as a component of the stems of Aglaia abbreviata. Another two compounds of this type 493 and 494 were isolated from the fruits of Ligustrum lucidum.

One lanostane peroxide 5α,8α-peroxydehydrotumulosic acid 495 was isolated from the epidermis of the sclerotia of Poria cocos. Additional two compounds of this type, isoterpenes C 496 and E 497, were discovered from the sclerotia of Inonotus obliquus. The leaves of Melissa officinalis was the source for two antiproliferative norlupane triterpenes 498 and 499. The aerial roots of Ficus microcarpa afforded another norlupane triterpene 500.

One novel 29-nor-3,4-seco-cycloartane triterpene methyl ester 501 was isolated from the aerial parts of Antirhea acutata, which showed moderate inhibitory activities in cyclooxygenase-1 and -2 assays. Phytochemical investigation of the leaves of Markhamia lutea resulted in the isolation of two cycloartane triterpenoids, musambins A 502 and B 503, as well as corresponding xylosides, musambiosides A 504 and B 505. These compounds showed anti-plasmodial and anti-trypansomal activity. Combretum quadrangularare contained a novel cycloartane-type triterpene named methyl quadrangularate B 506 that exhibited potent cytotoxicity with
The aerial roots of *Ficus microcarpa* afforded two oleanane triterpenoids 508 and 509. The structures of 508 was further confirmed by X-ray crystallography. Another compound of this class, sarmentolin 510, was identified as a hepatoprotective agent from *Sedum sarmentosum*. A glutinane triterpenoid 511 was identified as a component of the aerial parts of *Maytenus apurimacensis*. Aceranol acetate 512 was a 5,6-cleaved glutinane derivative from *Acer mandshuricum*.

A peroxyl-multiflorane triterpene ester 513 has been isolated from the processed seeds of *Trichosanthes kirilowii*. The plant *Azadirachta indica* contained a tetranortriterpenoid, 4α-hydroperoxy-6-O-acetynimbandiol 514. The absolute configuration of known longilene peroxide, isolated from the wood of *Eurycoma longifolia*, has been established by total synthesis.

Two euphane hydroperoxides, meliasenins A 515 and C 516, were isolated from the stem bark of *Melia toosendan*. Further members of this type, meliasenins I–O 517–523, were obtained from the fruits of the same plant. The relative configuration of 517 was further confirmed by single-crystal X-ray diffraction analysis. Another two species of this genus, *M. dubia* and *M. azedarach*, contained meliastatin 524 and 25-hydroperoxytirucalla-7,23(24)-diene-3,6-dion-21,16-olide 525, respectively. Meliastatin exhibited significant inhibition of the P388 cancer cell line. The roots of *Euphorbia micractina*
afforded further euphane/tirucallane derivatives 526–530. Three 3(4),9(10)-disecocycloartane peroxy triterpene lactones, pseudolarolides Q, T1, T2, and T3, were discovered from the seeds of *Pseudolarix kaempferi*. The leaves of the same species contained three more triterpene peroxides, pseudolarolides Q–S. The stereochemical structures of these compounds were confirmed by single-crystal X-ray analyses. One triterpene dilactones with a rare rearranged pentacyclic skeleton, longipedlactone K, was found from the stems of *Kadsura ananosma*. A cytotoxic triterpenoid schinalactone A, an endoperoxide with an unusual contracted ring A, has been isolated from the roots and stems of *Schisandra sphenanthera*, which showed significant cytotoxicity against PANC-1 cell lines with an IC_{50} value of 5.9 μM. The structure of a non-peroxic metabolite, named podocarpaside E, has been revised to 539 on the basis of an X-ray analysis.

3.5 Others: The structurally novel antiproliferative metabolite designated hexacyclinol 540 was first described by Gräfe and co-workers from basidiospores collected from *Panus rudis* growing on dead betula woods in Siberia. The structure of hexacyclinol was subsequently revised, and an alternative structure 541 was confirmed via total synthesis. In addition, an X-ray crystal structure was obtained, providing unequivocal structural confirmation. The first peroxide among the prenylated benzophenones, plukenetione C 542, was reported from the fruits of *Clusia plukenetii*. Continuing investigations of the plant yielded two further related prenylated benzophenone derivatives, 33-hydroperoxysampsones A and B 543, and F 544. Another two compounds of this type, peroxysampsones A 545 and B 546, were isolated from the roots of the Chinese medicinal plant *Hypericum sampsonii*, of which peroxysampson A showed comparable activity with norfloxacin against a NorA over-expressing multidrug-resistant (MDR) strain of *Staphylococcus aureus* SA-1199B. 550
A neurofibromatosis type 1 (NF1)-based bioassay-guided phytochemical investigation on Zanthoxylum armatum collected in Nepal led to the isolation of two isomeric timuramides A 547 and B 548, both of which can inhibit growth of NF1-defective tumor cell line at noncytotoxic concentrations.\(^{521}\) One antibacterial acylphloroglucinol, olympicin D 549, was isolated and characterized from the aerial parts of Hypericum olympicum.\(^{322}\) A hydroperoxyquinoline alkaloid, glycopentaphyllone 550, was reported from the fruits of Glycosmis pentaphylla, whose absolute configuration was established by applying Mosher’s method.\(^{323}\)

Walsuronoid A 551 was the first limonoid with a peroxide linkage from Walsura robusta. The structure of walsuronoid A was also confirmed by X-ray analysis.\(^{324}\) The stems of Khaya anthotheca afforded one further limonoid 552,\(^{325}\) and the related xylocarpin G 553 was obtained from the Chinese mangrove plant, Xylocarpus granatum.\(^{326}\) Additional member of the group, munronoid F 554, was discovered from Munronia unifoliolata.\(^{327}\)

Two unprecedented spiroketal peroxides, chloropupukeanolides A 555 and B 556, were isolated from an endophytic fungus Pestalotiopsis fici, with chloropupukeanolide A showing significant anti-HIV-1 and cytotoxic effects. A possible biosynthetic pathway to chloropupukeanolides A and B has been proposed.\(^{328}\) A cytotoxic prenylated flavone, named artoindonesianin B 557, was obtained from the root of Artocarpus champeden.\(^{329}\) The root of Zanthoxylum zanthoxyloides provided an aromatic peroxide 558.\(^{330}\)

A peroxy acid urticic acid 559 was discovered from the whole plant of Lescas articifolia.\(^{531}\) A spiranoid withanolide 560 was obtained from the leaves of Jaborosa odonelliana.\(^{332}\)
The stems of *Millettia taiwaniana* contained one isoflavonoid peroxide millewanin E 561. Brasixanthone C 562 was identified as a constituent of the stem bark of *Calophyllum brasilienses* collected in Brazil. One lignan tiegusanin M 563 was a constituent of the aerial parts of *Schisandra propingua*. The unique neolignan mansoxetane 564, isolated from the heartwood of *Mansonia gagei*, is the first example of a biphenylneolignan with a dioxetane ring discovered in nature.

Two prenylated polyketides, harrisotones C 565 and D 566 representing a rare spirocyclic skeleton, along with a cytotoxic hydroperoxypolyketide harrisonol A 567, were isolated from *Harrisonia perforata*. Two butanolides, litseadoxanins A 568 and B 569 bearing a 1,2-dioxane moiety, were obtained from the stem bark of *Litsea akoensis*. Chemical investigation of the leaves of *Machilus japonica* resulted in the isolation of apigenosylides A–C 570–572, which possess an unprecedented skeleton comprising the...
adduct of a butenolide moiety and apigenin glycoside linked via a 1,2-dioxane moiety. Apigenosylides B–C possess moderate inhibitory activity against \( \alpha \)-glucosidase.\(^{339}\) High-throughput natural products chemistry methods have facilitated the isolation of a beilschmiedic acid peroxide beilschmiedic acid N \( 573 \) from the leaves of a Gabonese species of *Beilschmiedia*, which may be an artifact of isolation formed through Diels-Alder addition of singlet oxygen.\(^{340}\) A cyclic peroxide named kramecyne \( 574 \) with good anti-inflammatory activity has been isolated from *Krameria cytisoides*.\(^{341}\)

Xanthoangelol \( E \), originally obtained from the root of *Angelica keiskei*,\(^{342}\) showed the effects of xanthoangelol, on NF-\( \kappa \)B activation and ET-1 gene expression in cultured porcine aortic endothelial cells.\(^{343}\) Two furanocoumarins, melicotriphyllins B \( 575 \) and D \( 576 \) bearing a hydroperoxy group on the geranyloxy side chain, were isolated from the
fruits of *Melicope triphylla*.\(^{344}\)

Two rare four-membered peroxide-containing phaeophytin, bidenphytins A \(^{577}\) and B \(^{578}\), were identified from *Biden pilosa*, a popular Taiwanese folk medicine. Possible biosynthetic pathways for them has been proposed.\(^{345}\) Bioassay-guided fractionation of the extract from *Kielmeyera coriacea* afforded a novel \(\delta\)-tocotrienol peroxy-dimer \(^{579}\).\(^{346}\) Two dimeric anthrone peroxides, adxanthromycins A \(^{580}\) and B \(^{581}\), were new inhibitors of ICAM-1/LFA-1 mediated cell adhesion molecule isolated from the fermentation broth of an
undescribed *Streptomyces* species. The aerial parts of the medicinal plant *Clerodendrum bungei* afforded additional peroxide dimer named bungein A 582. Clausamine G 583 containing a hydroperoxy moiety in the molecule, is the first example of the isolation of a peroxy-

\[ \text{Diagram of compounds 531-546} \]
ated carboxylate alkaloid in nature. The leaves of *Piper aduncum* afforded an prenylated benzoic acid derivative with antifungal activity whilst the related was obtained from the aerial parts of *Aster spathulifolius*. The presence of a hydroperoxide group at the side chain could be directly associated to its fungitoxicity.

Bioactivity-guided fractionation of the extract from *Piper crassinervium* afforded one prenylated hydroquinone.

The buds of *Lonicera japonica* contained a novel cyclic peroxide named shuangkangsu with significant antiviral activities, whose absolute stereochemistry was determined by CD analysis.

Echinobithiophene A, a peroxide bithiophene with significant antimicrobial activity, was isolated from *Echinops ritro*, and its structure was identified by spectral analysis including 2D NMR, and comparison of optical rotation values and chemical shifts of 13C NMR between the predicted and experimental data.

A pyrrolidone peroxide cucubalactam has been reported from *Cucubalus baccifer*. A mutualist actinomycete of the southern pine beetle, *Dendroctonus frontalis*, produced a polynene peroxide, mycangimycin, with pronounced antifungal activity. Its absolute configuration was determined by chemical modification followed by the modified Mosher method. The stem bark of the African tree *Antiaris africana* afforded a cardiac glycoside africanoside, which effected a concentration-dependent inhibition of tumor cell growth with a mean IC50 value of 5.3 nM.

4 Steroidal Peroxides

The ubiquitous ergosterol peroxide continued to be isolated from any number of sources, marine as well as terrestrial, particularly mushrooms. The diverse biological activities have been attributed to ergosterol peroxide. Ergosterol peroxide was found to be an inhibitor to the proliferation of K562, Jurkat, WM-1341, HL-60, and RPM1-8226 tumor cell lines by 10 to 40% at 10 μg/mL. Ergosterol peroxide from
the marine sponge *Spirastrella abata* showed cytotoxicity against several human solid tumor cell lines, and also against human gastric tumor cell line (SNU-1), human hepatoma cell line (SNU-354), human colorectal tumor cell line (SNU-C4), and murine sarcoma-180 were 18.7, 158.2, 84.6 and 74.1 μM (IC₅₀), respectively. Ergosterol peroxide from two species of the *Pleurotus* genus, *P. eryngii* and *P. ostreatus*, exhibited osteoclastogenesis inhibitory and trypanocidal activity, respectively. Ergosterol peroxide was obtained for the first time from *Oryza sativa* in 2006. This is the first report of potential allelopathic activity of steroids on weeds based on their phytotoxicity on barnyardgrass (*Echinochloa crus-galli*) as target species. Ergosterol peroxide was found to be a DNA topoisomerase I inhibitor, and exhibit potent of rat lens aldose reductase inhibition. Among the lipophilic extracts of seven traditional edible mushrooms, the acetone extract of *Sarcodon aspratus* markedly inhibited the growth of HL60 human leukemia cells and induced apoptosis after 24 h incubation. The major active component was identified as ergosterol peroxide. It is completely inhibited growth and induced apoptosis of HL60 cells at a concentration of 25 μM. Anti-inflammatory activity has been found for ergosterol peroxide isolated from several species. Ergosterol peroxide also displayed strong anticomplement activity on the classical pathway with IC₅₀ values of 126.8 μM. In addition, the antimicrobial, antituberculosis, and melanogenesis inhibitory effects of ergosterol peroxide have also been reported.

In addition to ergosterol peroxide, a number of other steroidal endoperoxides have been reported, which are most commonly 5α,8α-epidioxysterols with variations in the side chains. A 5α,8α-epidioxysterol sulfate 592 was isolated from the cultured diatom *Odontella aurita*. Four steroidal saponins, pariposides A–D 593–596, were isolated from the roots of *Paris polyphyilla*. These compounds are the first spirostanol saponins with a peroxy group located between C-5 and C-8 of the aglycon. Bioassay-guided fractionation of an...
Extract of a marine sponge, *L. edodes*, has led to the isolation and identification of new epidioxy steroids. In addition, several new 5α-epidioxy steroids have also been isolated from a marine sponge. The marine sponge, *L. edodes*, was found to be a valuable source for two new sterols, *A. peroxysteryl*, and its C-6 epimer. The marine sponge, *L. edodes*, was isolated from a marine sponge, *A. peroxysteryl*, sp. from the bryozoan *B. epidermysterols* (Lichadonissia Is., Greece) provided another group of the sponge during sample storage and extraction. Furthermore, a pair of 5α-epidioxy steroids, 618, was isolated from the marine sponge, *A. peroxysteryl*, sp. from the bryozoan *B. epidermysterols*. A peroxy steroid, 9(11)-dehydroxyaxinysterol, was isolated from the marine sponge, *A. peroxysteryl*, sp. from the bryozoan *B. epidermysterols*.
type steroid sclerosteroid E 633 was a constituent of the soft coral *Scleronephthya gracillimum*. A chemical investigation of the roots of *Cynanchum stauntonii* has resulted in the characterization of a new hydroperoxide with a 13,14:14,15-disecopregnane-type skeleton, named stauntonine 634, whose relative stereochemistry was determined by X-ray crystallographic diffraction analysis. The compound showed dose-dependent relaxation on aortic rings with endothelium contracted by phenylephrine or KCl.

The structures of a series of peroxy function containing pregnane glycosides including periperoxides A–E 635–639 and previously reported periplocosides A–K 639,640 have been revised to be orthoester group bearing ones using 2D NMR techniques as well as chemical transformations and X-ray crystallographic diffraction analysis.

5 Fatty Acid Metabolites

Lipoxygenase (LOX) pathways are involved in the
production of important signal and defensive metabolites in mammals, higher plants, and algae. In these pathways molecular oxygen is introduced into a polyunsaturated fatty acid to form an intermediate hydroperoxide, which may then be cleaved to give shorter chain-length oxygenated products, collectively known as oxylipins. Interestingly, different principles of transformations have been identified. While plants use almost exclusively C18 fatty acids for the production of oxylipins, algae and animals rely predominantly on the transformation of C20 fatty acids. In animals cleavage of the intermediate hydroperoxy fatty acids is achieved by a dual function of LOXes, while plants and algae rely often on hydroperoxide lyases (HPLs) to produce shorter chain oxylipins.

The mechanism of fatty acid transformation in the Diatom Thalassiosira rotula does not, however, follow established lipoxygenase/hydroperoxide lyase pathways known from higher plants or mammals but rather relies on a unique transformation of polyunsaturated hydroperoxy fatty acids. These intermediates are then transformed to polyunsaturated short chain aldehydes and short chain hydroxylated fatty acids, which are novel oxylipins. The similar transformation mechanism of fatty acid hydroperoxides has also been reported.
from the moss *Physcomitrella patens*. The moss produces metabolites typical for animals, plants, algae, and mushrooms by new transformations of arachidonic acid, combining in a unique way metabolic themes from all these organisms. Recent genome sequences leading to an increasing number of enzyme-mechanistic and structural analysis of LOXs and new members of the oxylipin pathway, as well as oxylipin profiling shed new light on the biosynthesis and occurrence of oxylipins in non-mammalian organisms. A review of these new aspects has been published.

6 Conclusions

This article reviewed several hundreds of new peroxy natural products produced by terrestrial fungi, higher plants, and marine organisms not only their structures and chemistry, but also their diverse biological activities. However, only a limited number of them have been further evaluated since a limited supply of the active ingredients from the natural sources. It needs more research attention on total synthesis of important compounds and further biological evaluation. Further studies on their previously untapped resources with further unprecedented bioactive metabolites needs to be conducted. This review also emphasizes the role of peroxides from terrestrial fungi, higher plants, and marine organisms as an important source of leads for drug discovery.

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