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Bioactive Fungal Endoperoxides

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Abstract

The present review describes research on rare endoperoxides isolated from terrestrial and marine fungi, lichenized fungi and fungal endophytes. More than thirty fungal metabolites have been confirmed to exhibit antimicrobial, antibacterial, and anticancer activities, as well as other activities. A wide spectrum of pharmacological activities is associated with this type of fungal metabolites, which is also true for selected synthetic derivatives.

Keywords: Endoperoxides; Fungi; Fungal endophytes; Lichens; Activities

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Introduction

More than 900 endo-peroxides and hydroperoxides have been isolated from natural sources, mainly as constituents of plants, and fungi, fungal endophytes; they also were found in algae, invertebrates, and other organisms [1-5]. Among naturally occurring endo-peroxides and hydroperoxides 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 antibacterial, antitumor, and mainly antimalarial agents [6-8]. The purpose of this review is to summarize bioactive metabolites of more than thirty natural endoperoxides, belonging to diverse structural classes: sterols, terpenes, aromatic compounds, and alkaloids.

This paper review new and active endo-peroxides produced by fungi, lichenized fungi, and fungal endophytes described their structures, chemistry, and pharmacological activities.

Sterols and its derivatives

Ergosterol peroxide {1} (**Figure 1**) has been detected in many fungi and fungal endophytes: *Claviceps purpurea* [ergot fungus], *Ganoderma lucidum*, *G. tsugae* and *G. sichuanense* [lingzhi mushrooms] [4,5], mushroom *Daedalea quercina* [4], *Piptoporus betulinus* [known as the Birch Bracket Mushroom], *Cryptoporus volvatus* [known as the Grey-Brown Sap Rot Mushroom] [5], *Guignardia laricina* [*Botryosphaeriales*], *Lampteromyces japonicus* [4], a necrotrophic fungus *Botrytis cinerea* [5], *Lactarius uvidus* [North American Milk-Cap Mushroom], *L. volemus*, *Cryptoporus volvatus* [known as the Grey-Brown Sap Rot Mushroom], *Aspergillus* sp., *A. niger, A. oryzae, A. flavus, A. terreus,* and *A. fumigatus* [5], *Fusurium monilforme, F. osysporum, Penicillium rubrum, P. sclerotigenum* [4], *Dictyonema glabratum*

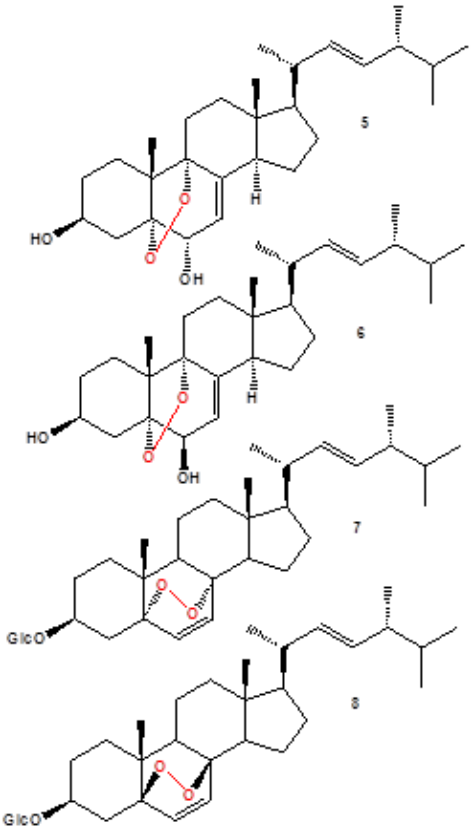

Figure 1 Ergosterol peroxides and derivatives.

[a lichen-forming *basidiomycete*], *Lasiosphaera nipponica, Gloeophyllum odoratum, Gymnopilus spectabilis, Hericium erinaceus* [Medicinal, Edible Mushroom], *Hypsizigus marmoreus, Inonotus obliquus, I. radiatus, 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], *P. ribis [*medicinal fungus], *P. torulosus* [known as P. 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] [5], and from the edible mushroom, *Volvariella volvacea* [9]. Ergosterol peroxide and its D-glucopyrano-side [2] were obtained from the methanol extract of *Cordyceps sinensis* [10,11]. The glycosylated form of ergosterol peroxide was found to be a greater inhibitor to the proliferation of K562, Jurkat, WM-1341, HL-60 and RPMI-8226 tumor cell lines [11]. Endophytic fungus No ZZF36 from a brown alga from the South China Sea, produced ergosterol peroxide {1}, along with brassicaterol, and ergosterol [12]. 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. Isolated endoperoxide {1} 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 chemo-preventive activities [13]. Ergosterol peroxide {1} 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 [14]. Endoperoxide {1} isolated from of the deep-sea derived fungus *Aspergillus species* CXCTD-06-6a showed activities against P388 and Hela cell lines [15]. Ergosterol peroxide {1} 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* [4,5]. Methanol extract of fungus *Tremella fuciformis* showed significant neuritogenic activity against PC12 cells. Two neuritogenic compounds ergosterol peroxide {1} and 5α,8α-epidioxy-[22*E*,24*R*]-ergosta-6,22-diene-3β-ol 3-O-β-D-glucopyranoside {2} were isolated and identified from the methanol extract of fungus *T. fuciformis* [16]. Same compounds were isolated from the fruiting bodies of the Chinese toxic mushroom *Naematoloma fasciculare* [17]. Two peroxides {3,4} (**Figure 1**) produced a camphor fungus *Antrodia camphorata* [known as Niu-Chang in Taiwan] [18]. Compound {5} 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* [19]. Two sterols {5,6} (**Figure 2**) were isolated from the fruiting body of *Panellus serotinus* also known as Mukitake mushroom [family Mycenaceae]. Compound {6} was also isolated from other edible mushroom *Lepista nuda* [also known as blewit, syn. *Clitocybe nuda*] [20]. Ergostane-type endoperoxy glycosides {7,8} were isolated [21] from the ethanol extract of an attractive mushroom *Lactarius volemus* [family *Russullaceae]* which inhibits the growth of several tumor cell lines *in vitro* [22]. Asperversin A {9} (**Figure 3**) and ergosterol peroxide {1} 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* [23].

Terpenes and derivatives

Several nor-sesquiterpene peroxides (**Figure 4**), named as talaperoxide A {10}, B {11}, C {12}, and D {13}, were isolated from culture of fungi *Talaromyces* species HN21-3C [family *Trichocomaceae*]. Isolated compounds showed antineoplastic activity against mammary cancer, prostatic carcinoma, uterine cervix carcinoma or hepatic carcinoma [24,25]. Same compounds, talaperoxides A-D {10-13}, as well as one known analog, steperoxide B {14, or merulin A}, have been isolated from a *mangrove endophytic fungus*, *Talaromyces flavus* [26]. Talaperoxides {12} and {13} showed cytotoxicity against the five human cancer cell lines with IC_{50} values between 0.70 µg/ml and

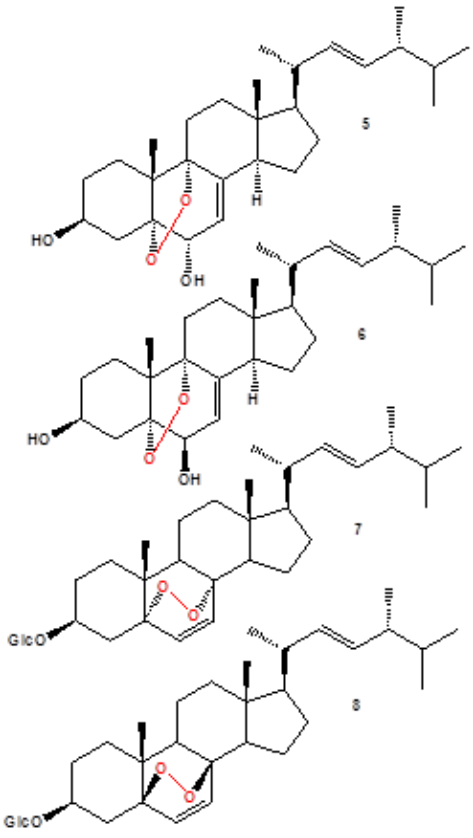

Figure 2 Sterol endoperoxides.

2.78 µg/ml. Chamigrane-type metabolites named steperoxides A {14}, B {15}, C {16} and D {17}, have been isolated from the hydnoid fungus *Steccherinum ochraceum* [Phanerochaetaceae]. Compounds {15,17} showed significant antimicrobial activity against *Staphylococcus aureus* at 10 µg/disk and 5 µg/disk [27-29]. Semi-synthetic derivative {18} (**Figure 5**) of the fugally-derived natural product {12} showed the antiparasitic and cytotoxic activity [IC_{50}=0.043 µM vs. *T. brucei*; IC_{50}=13 µM vs. Hela cells], respectively [30]. Previously, the same nor-chamigrane endoperoxide, named as merulin A [syn. steperoxide B, {15}, B {19}, C {20}, and D {21} (**Figure 6**), were isolated from the culture broth extract of an endophytic fungus of *Xylocarpus granatum.* Same compounds were isolated from the endophytic fungus

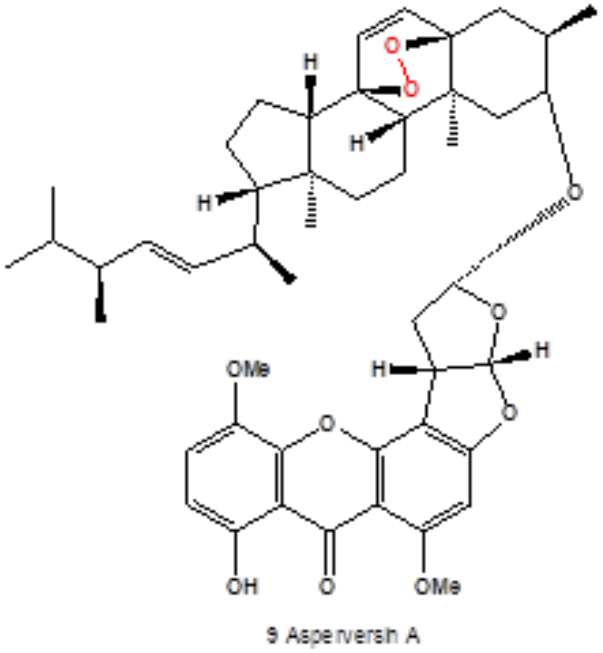

Figure 3 Antibacterial metabolite.

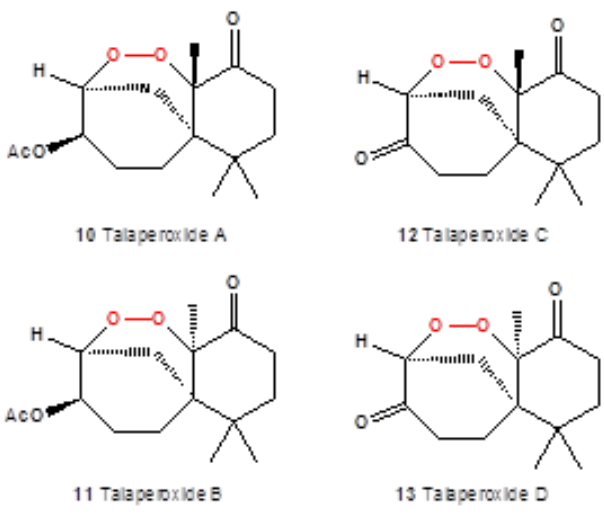

Figure 4 Nor-sesquiterpene peroxides.

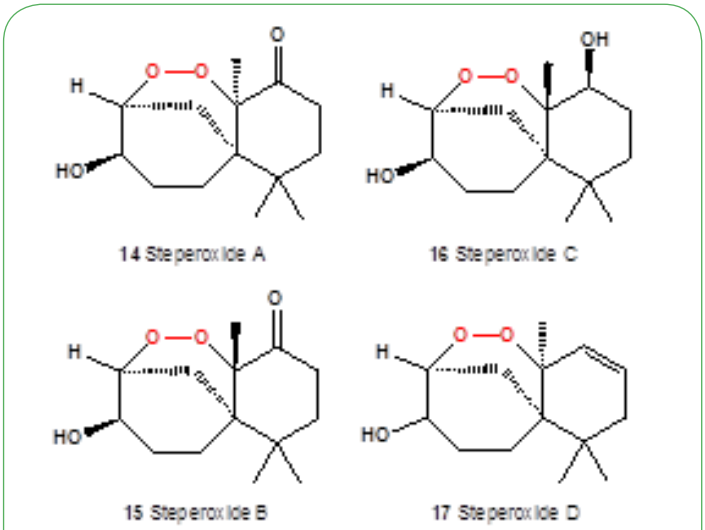

Figure 5 Steperoxide endoperoxides.

Talaromyces flavus isolated from the mangrove plant *Sonneratia apetala* [26]. Metabolites 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 [31]. Cytosporolides A {22}, B {23}, and C {24} (**Figure 7**), caryophyllene-derived meroterpenoids with a unique peroxylactone skeleton, were isolated from cultures of the fungus *Cytospora* species. All cytosporolides showed significant antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pneumoniae* {24}. Also, compound {24} showed good activity in vitro against dermatophytic fungi and moderate activity against *C. albicans* and *S. aureus*.

Aromatic endoperoxides

Hypocrellins are dark red pigments having the perylenequinone structure, with photodynamic activity toward microorganisms. These pigments produced by the fungus *Hypocrella bambusae* [32,33], and a parasitic fungus *Shiraia bambusicoia* [34-36]. All isolated metabolites have shown anticancer activities [34,37,38], and antiviral activity against the human immunodeficiency virus [HIV-1] [39]. Natural cytotoxic peroxyhypocrellin {25} (**Figure 8**) was isolated from *S. bambusicoia* [40]. Rare dimeric anthrone peroxide, named oxanthromicin {23} (**Figure 9**), an antibiotic isolated from an *Actinomadura* species SCC 1646 fermentation broth [41,42]. Adxanthromycins A {24} and B {25} were new inhibitors of ICAM-1/LFA-1 mediated cell adhesion molecule isolated from the fermentation broth of *Streptomyces* species NA-148. Adxanthromycins A and B inhibited the formation of the JY cell aggregates from 1.5 mg/ml, respectively, in a dose-

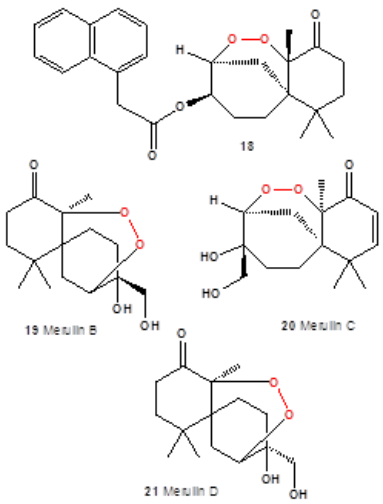

Figure 6 Stepero Merulin endoperoxides. xide endoperoxides.

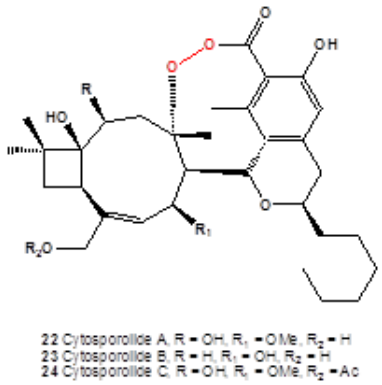

Figure 7 Meroterpenoid endoperoxides.

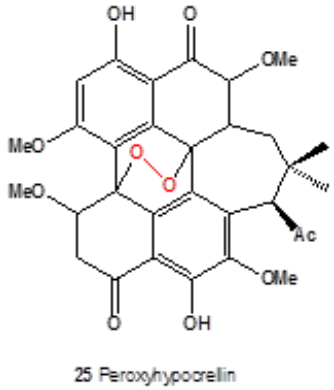

Figure 8 Cytotoxic endoperoxide.

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 IC_{50} of 18.8 µg/ml and 25.0 µg/ml, respectively [43,44].

Spiroketal endoperoxides

Chloropupukeanolides A {29} (**Figure 10**) and B {30},

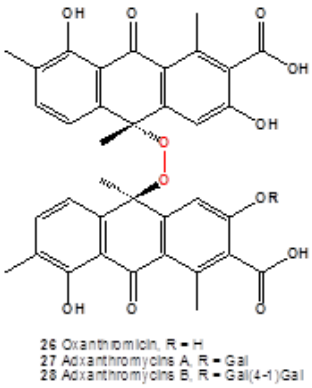

Figure 9 Dimeric endoperoxides.

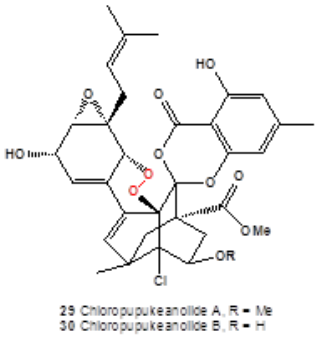

Figure 10 Spiroketal endoperoxides.

unprecedented spiroketal peroxides, two highly functionalized metabolites featuring a chlorinated pupukeanane core, were isolated from an endophytic fungus *Pestalotiopsis fici.* The compound {29} was reported to have anti-HIV and anti-cancer activities with an inhibitory effect on HIV-1 replication in C8166 cells of 6.9 µM [EC_{50} value] and IC_{50} values of 16.9, 15.5, and 15.9 µM against Hela, MCF-7, and MDA-MB-231 cell lines, respectively [45].

Alkaloid endoperoxides

Bioactive endoperoxide verruculogen {31} (**Figure 11**) for the first time was isolated from a strain of *Penicillium verruculosum* isolated from peanuts [46]. This compound {31} had also been isolated from a number of other microbiological sources including *Aspergillus caespitosus* [47], *A. fumigatus* [48], *A. fischeri* [49], *Penicillium piscarium* [50], *P. paxilli* [51], *P. piceum, P. nigricans, P. raistrickii* [50], *P. estinogenum* [52], *P. simplicissmum* [53], *Eupenicillium* sp. [54], and an invasive fungal pathogen *Neosartorya fischeri [A. fischerianus]* [55]. A tremorgenic mycotoxin verruculogen {31} is a potent inhibitor of high conductance Ca activated K [maxi-K] channel, other pharmacological effects of {31} have also been reported [56]. The acetoxy derivative {32} has been isolated from Penicillium verruculosum [57]. More recently, verruculogen {31} and fumitremorgin B were found in several strains of the genus *Aspergillus: A. lentulus, A. udagawae,* and *A. viridinutans* [58]. In addition, of eighteen that exerted moderate lethality toward brine shrimps, verruculogen {31} showed significant toxicities with median lethal concentration [LC_{50}] values of 13.6 µg/ml

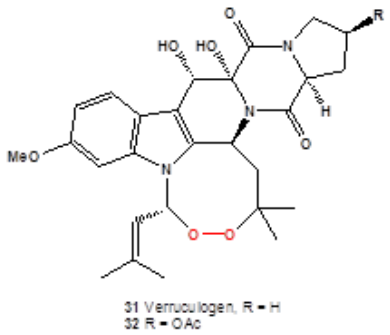

Figure 11 A tremorgenic mycotoxin.

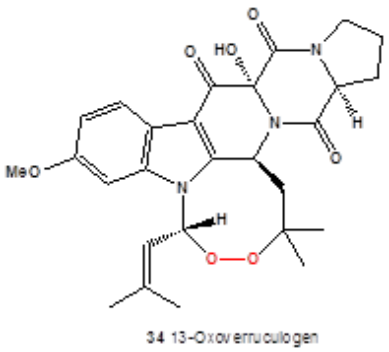

Figure 12 Alkaloid endoperoxides.

[59]. Other endoperoxide, neurotropic mycotoxin fumitremorgin A {33} (**Figure 12**), was recovered from a strain of *Aspergillus fumigatus* [60,61]. Fumitremorgin A {33} known as neurotropic metabolite [62] was produced by fungus *Aspergillus fumigatus* [63]. Diketopiperazine alkaloid, 13-oxo-verruculogen {34}, had been obtained from the fermentation of *Aspergillus fumigatus* from a holothurian, *Stichopus japonicus* [Lingshan Island, Qingdao, China] [64].

Conclusion and Perspectives

During the last 25 years, there has been an unprecedented growth in the chemistry of natural as well as synthetic peroxides [1-5,8,65-71]. 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 helminthic infections. In medicinal chemistry of peroxides, for example, ascaridole and qinghaosu [known as artemisinin] a natural peroxides exhibiting high antimalarial activity [65,66,70], is the most important drug in use for approximately 25 years. This review also emphasizes the role of endoperoxides from fungi, lichens, and fungal endophytes as an important source of leads for drug discovery.

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