Antiprotozoal and Antitumor Activity of Natural Polycyclic Endoperoxides: Origin, Structures and Biological Activity

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Abstract: Polycyclic endoperoxides are rare natural metabolites found and isolated in plants, fungi, and marine invertebrates. The purpose of this review is a comparative analysis of the pharmacological potential of these natural products. According to PASS (Prediction of Activity Spectra for Substances) estimates, they are more likely to exhibit antiprotozoal and antitumor properties. Some of them are now widely used in clinical medicine. All polycyclic endoperoxides presented in this article demonstrate antiprotozoal activity and can be divided into three groups. The third group includes endoperoxides, which show weak antiprotozoal activity with a reliability of up to 70%, and this group includes only 1.1% of metabolites. The second group includes the largest number of endoperoxides, which are 65% and show average antiprotozoal activity with a confidence level of 70 to 90%. Lastly, the third group includes endoperoxides, which are 33.9% and show strong antiprotozoal activity with a confidence level of 90 to 99.6%. Interestingly, artemisinin and its analogs show strong antiprotozoal activity with 79 to 99.6% confidence against obligate intracellular parasites which belong to the genera Plasmodium, Toxoplasma, Leishmania, and Coccidia. In addition to antiprotozoal activities, polycyclic endoperoxides show antitumor activity in the proportion: 4.6% show weak activity with a reliability of up to 70%, 65.6% show an average activity with a reliability of 70 to 90%, and 29.8% show strong activity with a reliability of 90 to 98.3%. It should also be noted that some polycyclic endoperoxides, in addition to antiprotozoal and antitumor properties, show other strong activities with a confidence level of 90 to 97%. These include antifungal activity against the genera Aspergillus, Candida, and Cryptococcus, as well as anti-inflammatory activity. This review provides insights on further utilization of polycyclic endoperoxides by medicinal chemists, pharmacologists, and the pharmaceutical industry.

Keywords: antiprotozoal; antitumor; polycyclic; peroxides; pharmacological potential; PASS

1. Introduction

Polycyclic endoperoxides are a rare group of naturally occurring metabolites found in various parts of plants such as leaves, roots, bark, stems, seeds, fruits, and flowers [1–17]. In addition, they have been found in extracts of various types of marine invertebrates and algae, and endoperoxides are synthesized by various types of fungi, fungal endophytes, and other microorganisms [8,9,13–15,18–20].

As shown in recent years, many polycyclic endoperoxides, both natural and synthetic, have antimalarial effects [21,22]. It is known that malaria or “swamp fever” refers to a group of transmissible infectious diseases transmitted to humans by bites of female mosquitoes belonging to the genus Anopheles, caused by parasitic protists of the genus Plasmodium, mainly P. falciparum [23–25]. According to the WHO World Malaria Report,
at the beginning of the 21st century, the incidence ranged from 350 to 500 million cases per year, of which 1 to 3 million ended in death [26,27]. In connection with these ominous data, any new sources of natural antimalarial agents are of great interest to medicine and pharmacology, as well as to the pharmaceutical industry [28–30].

In this review, we will look at rare and unusual polycyclic endoperoxides isolated from different terrestrial and marine sources. The biological activity of many polycyclic endoperoxides has not been determined, and we present the pharmacological activities detected experimentally and predicted based on the structure-activity relationships using the PASS (Prediction of Activity Spectra for Substances) software [31–33]. PASS estimates the probabilities of several thousand biological activities with an average accuracy of about 96%. Probability of belonging to the class of “actives” Pa is calculated for each activity, providing the assessment of the hidden pharmacological potential of the investigated natural polycyclic endoperoxides [2,7,13,14,17,31–33].

2. Polycyclic Endoperoxides Derived from Marine Sources

Marine algae (both microalgae and macrophytes) and invertebrates are the main source of biologically active secondary metabolites, which include hydrocarbons, terpenoids, lipids, steroids, carotenoids, aromatic compounds, and alkaloids, as well as mixed compounds containing heteroatoms and polycyclic endoperoxides [2,4–8,17–20,34–64].

A series of polycyclic peroxides such as contrunculin B (1) as well as the trunuclin peroxides (2–7) were discovered in the extracts of Australian marine sponge Latrunculia conulosa [65], Latrunculia sp. [66] and found in an Okinawan sponge Sigmosceptrella sp. [67]. Structures (1–16) can be seen in Figure 1, and their biological activity is presented in Table 1. Two unusual endoperoxide diterpenoids (8 and 9) were isolated from the brown seaweed Taonia atomaria [68]. Cytotoxic 8,11-epidioxy-7-hydroxy-3,12,15(17)-cembratrien-16,2-olide called cembranolide C (or denticulatolide, 10) known as icthyotoxin was found in soft corals Lobophytum denticulatum, Sinularia mayi, and Sarcophyton crassocaule and its acetate (11) was also found in L. denticulatum extract [69–72].

Table 1. Biological activity of natural polycyclic peroxides derived from marine sources.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|------------------------------|------------------------------------------|----------------------------------------|
| 1  | Antiprotozoal (Plasmodium) (0.941) Anti-inflammatory (0.963) | | |
| 2  | Antiparasitic (0.812) Antineoplastic (0.722) Anti-helmintic (0.761) | | |
| 3  | Antiprotozoal (Plasmodium) (0.735) Antimetastatic (0.625) Antifungal (0.702) | | |
| 4  | Antiparasitic (0.812) Antineoplastic (0.722) Anti-helmintic (0.761) | | |
| 5  | Antiprotozoal (Plasmodium) (0.735) Antimetastatic (0.625) Antifungal (0.702) | | |
| 6  | Antiparasitic (0.823) Antineoplastic (0.741) Anti-helmintic (0.731) | | |
| 7  | Antiprotozoal (Plasmodium) (0.714) Antimetastatic (0.633) Antifungal (0.673) | | |
| 8  | Antiparasitic (0.806) Antineoplastic (0.755) Anti-helmintic (0.832) | | |
| 9  | Antiprotozoal (Plasmodium) (0.742) Antimetastatic (0.681) Antifungal (0.689) | | |
| 10 | Antiparasitic (0.786) Antineoplastic (0.722) Anti-helmintic (0.774) | Alzheimer’s disease treatment (0.745) Neurodegenerative diseases treatment (0.662) | |

*Pa estimates the probabilities of several thousand biological activities with an average accuracy of about 96%.
Table 1. Cont.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|--------------------------------|------------------------------------------|----------------------------------------|
| 11 | Antiprotozoal (Plasmodium) (0.802) | Antineoplastic (0.983) | Alzheimer’s disease treatment (0.722) |
| 12 | Antiprotozoal (Plasmodium) (0.844) | Antineoplastic (0.921) | Antileukemic (0.599) |
| 13 | Antiprotozoal (Plasmodium) (0.835) | Antineoplastic (0.912) | Antileukemic (0.602) |
| 14 | Antiprotozoal (Plasmodium) (0.829) | Antineoplastic (0.915) | Antileukemic (0.599) |
| 15 | Antiprotozoal (Plasmodium) (0.948) | Antineoplastic (0.835) | Anti-inflammatory (0.576) |
| 16 | Antiparasitic (0.542) | Antimetastatic (0.635) | Anti-inflammatory (0.576) |

* Only activities with Pa > 0.5 are shown.

Figure 1. Bioactive polycyclic endoperoxides derived from marine sources.
Norditerpenoid, aplypallidioxone (12) was detected in Australian encrusting sponge *Aplysilla pallida* [73], and two abietic acids (13 and 14) that were previously found in plants have also been found in green algae *Elodea canadensis* [74].

A guaiane-type sesquiterpene, 1,7-epidioxy-5-guaiene (15) was found and later isolated from *Axinyssa* sponge [75], and an oxygenated sesquiterpenoid, 1,7-epidioxy-5-guaien-4-ol called peroxygibberol (16), was isolated from a Formosan soft coral, *Sinularia gibberosa*, which demonstrated moderate cytotoxicity toward a human liver carcinoma cell line [76]. Structures (16–35) can be seen in Figure 2, and their biological activity is presented in Table 2.

![Figure 2. Bioactive polycyclic endoperoxides derived from marine sources.](image-url)
Table 2. Biological activity of natural polycyclic peroxides derived from marine sources.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|---------------------------------|------------------------------------------|------------------------------------------|
| 17 | Antiprotozoal (Plasmodium) (0.925) | Apoptosis agonist (0.961) Antineoplastic (0.889) | Atherosclerosis treatment (0.734) Immunosuppressant (0.721) |
| 18 | Antiprotozoal (Plasmodium) (0.889) | Apoptosis agonist (0.867) Antineoplastic (0.841) Antimetastatic (0.611) | Anti-inflammatory (0.815) Anti-ulcerative (0.736) |
| 19 | Antiprotozoal (Plasmodium) (0.838) | Apoptosis agonist (0.977) Chemopreventive (0.942) Antineoplastic (0.915) Antiparkinsonian, rigidity relieving (0.711) | Atherosclerosis treatment (0.911) Hypolipemic (0.836) Lipoprotein disorders treatment (0.826) Anti-hypercholesterolemic (0.802) Prostate cancer treatment (0.687) |
| 20 | Antiprotozoal (Plasmodium) (0.798) | Apoptosis agonist (0.943) Antineoplastic (0.767) | Atherosclerosis treatment (0.738) Lipoprotein disorders treatment (0.587) |
| 21 | Antiprotozoal (Plasmodium) (0.694) | Apoptosis agonist (0.961) Chemopreventive (0.733) Antineoplastic (0.731) | Atherosclerosis treatment (0.628) Anti-fungal (0.635) |
| 22 | Antiprotozoal (Plasmodium) (0.839) | Apoptosis agonist (0.854) Antineoplastic (0.832) | Anti-inflammatory (0.809) Anti-ulcerative (0.721) |
| 23 | Antiprotozoal (Plasmodium) (0.871) | Chemopreventive (0.931) Antineoplastic (0.919) | Atherosclerosis treatment (0.907) Anti-hypercholesterolemic (0.788) |
| 24 | Antiprotozoal (Plasmodium) (0.819) | Apoptosis agonist (0.956) Chemopreventive (0.933) Antineoplastic (0.905) | Atherosclerosis treatment (0.899) Anti-hypercholesterolemic (0.823) |
| 25 | Antiprotozoal (Plasmodium) (0.822) | Apoptosis agonist (0.966) Antineoplastic (0.929) Prostate cancer treatment (0.699) | Atherosclerosis treatment (0.919) Hypolipemic (0.822) Lipoprotein disorders treatment (0.814) |
| 26 | Antiprotozoal (Plasmodium) (0.712) | Apoptosis agonist (0.967) Antineoplastic (0.740) | Atherosclerosis treatment (0.635) Anti-fungal (0.623) |
| 27 | Antiprotozoal (Plasmodium) (0.713) | Apoptosis agonist (0.966) Antineoplastic (0.742) | Atherosclerosis treatment (0.636) Anti-fungal (0.624) |
| 28 | Antiprotozoal (Plasmodium) (0.776) | Apoptosis agonist (0.929) Antineoplastic (0.975) | Atherosclerosis treatment (0.721) Lipoprotein disorders treatment (0.632) |
| 29 | Antiprotozoal (Plasmodium) (0.778) | Apoptosis agonist (0.922) Antineoplastic (0.756) | Atherosclerosis treatment (0.714) Lipoprotein disorders treatment (0.599) |
| 30 | Antiprotozoal (Plasmodium) (0.711) | Apoptosis agonist (0.971) Antineoplastic (0.788) | Atherosclerosis treatment (0.623) Anti-fungal (0.644) |
| 31 | Antiprotozoal (Plasmodium) (0.699) | Apoptosis agonist (0.954) Antineoplastic (0.737) | Atherosclerosis treatment (0.699) Anti-fungal (0.676) |
| 32 | Antiprotozoal (Plasmodium) (0.778) | Apoptosis agonist (0.942) Antineoplastic (0.732) | Atherosclerosis treatment (0.667) Anti-fungal (0.645) |
| 33 | Antiprotozoal (Plasmodium) (0.778) | Apoptosis agonist (0.961) Antineoplastic (0.889) Proliferative diseases treatment (0.522) | Hypolipemic (0.854) Anti-eczemat (0.812) Atherosclerosis treatment (0.787) |
| 34 | Antiprotozoal (Plasmodium) (0.833) | Apoptosis agonist (0.856) Antineoplastic (0.838) | Anti-inflammatory (0.815) Anti-ulcerative (0.729) |
| 35 | Antiprotozoal (Plasmodium) (0.866) | Apoptosis agonist (0.849) Antineoplastic (0.839) | Anti-inflammatory (0.811) Anti-fungal (0.677) |

* Only activities with Pa > 0.5 are shown.
An extract of a marine sponge, *Lendenfeldia chondrodes* has led to the isolation and identification of two C-24 stereoisomers (17 and 18) of steroid, 5R,8R-epidioxy-24-hydroperoxycholesta-6,28(29)-dien-3α-ol. Obtained data with the molecular formula of steroid indicated that a hydroperoxy group and a vinyl group are attached at position-24 in both the *R*- and *S*-configurations [77], and cytotoxic steroid, (3β,5α,8α,24R,25R)-epidioxy-24,26-cyclocholesta-6,9(11)-dien-3-ol (19) was identified from *Tethya* sp. [78].

Interestingly, steroid, (3β,5α,8α)-epidioxycholesterol-6-en-3-ol (20) was found in three cone snail species, *Conus eburaeus*, *C. leopardus*, and *C. tessulatus* (family Conidae) [79], and was also present in the extract of polychaete worm *Perinereis aibuhitensis* [80], it was also isolated from the steroid fraction of sponges *Axinella cannabina*, *Luffariella cf. variabilis* [81,82], the tunicate *Cynthia savignyi* [83], and in long-spined sea urchin *Diadema setosum* [84]. Isolated steroid showed antibacterial, antifungal, and cytotoxic activities [81–84]. Detection of this steroid in various species of marine invertebrates could indicate that they all share a food chain, and the source of this steroid may be algae.

(3β,5α,8α)-Epidioxy-24-methylcholesta-6-en-3-ol (21) has been isolated from the several marine invertebrates, tunicate *Ascidia nigra*, pillar coral *Dendrogyra cylindrus*, marine sponge *Thalysias juniperina*, and sea hare *Aplysia dactylyoma* [85]; in addition, this steroid was found in the tunicates *Dendrodoa grossularia* and *Ascidia aspera*, the gastropoda *Aplysia depilans* and *Aplysia punctata* [86], the sea anemone *Metridium senile* [87], and the sponge *Tethya aurantium* [88].

(3β,5α,8α,22E,24S)-Epidioxy-24-methylcholesta-6,22,25-trien-3-ol called axinysterol (22), (3β,5α,8α,24R)-Epidioxy-24-methylcholesta-6-en-3-ol (23) and (3β,5α,8α,22E,24R)-Epidioxyxystigmast-6,22-dien-3-ol (24) were detected in MeOH extract of the marine sponge *Luffariella cf. variabilis* [85].

22,23-Dihydro-5,8-epidioxyxystigmast-6-en-3-ol (25) was surrounded by *Luffariella cf. variabilis*, *Tethya sp.*, and sea squirt *Dendrodoa grossularia* [82,85–88]. (3β,5α,8α)-Epidioxy-22,23-cyclopropocholesta-6-en-3-ol (26) and (3β,5α,8α)-endoperoxy-23-demethylgorgost-6-en-3-ol (27) were discovered in soft corals *Sinularia maxima*, *S. gibberosa* and *Sinularia* sp. [89,90].

(3β,5α,8α,22E,24S)-Epidioxyergosta-6,9(11),22-trien-3-ol (28) was found in two tunicates *Ascidia nigra* and *Dendrogyra cylindrus* and sponge *Thalysias juniperina* [82,85,91], and (3β,5α,8α)-epidioxy-24-methylcholesta-6,9(11),24(28)-trien-3-ol (29) was detected in *Ascidia nigra* [85,88].

(3β,5α,8α,22E,24R)-Epidioxy-23,24-dimethylcholesta-6,22-dien-3-ol (30) was isolated from MeOH extract of the single-celled algae *Odontella aurita* [92], and it was also found in edible mushrooms *Lentinus edodes*, which are also known as shitake [93].

(3β,5α,8α,22E)-Epidioxy-24-norcholesta-6,22-dien-3-ol (31) was detected in the sea pen, opisthobranch mollusk *Virgularia sp.* [94], and in A. nigra, *D. cylindrus*, and *T. juniperina* [85]. (3β,5α,8α,24(28E))-Epidioxy-24-ethylcholesta-6,24(28)-dien-3-ol (32) has been isolated and structure elucidated from several tunicates, namely *Ascidia nigra* and *Dendrogyra cylindrus*, and (3β,5α,8α,24(28)Z)-form was detected in *Dendrodoa grossularia* [85,86].

Cytotoxic (3β,5α,8α,22E,24R)-epidioxyergosta-6,22-dien-3-ol (33), well-known as 5α,8α-peroxygerosterol, is the most widely distributed steroid in the plant kingdom, lichens and fungi [5,6], and it is also found in marine sponges *Axinella cannabina*, *Halichondria sp.*, *Suberites carnosus*, *Spirastrella abata*, *Thalysias juniperina* [85,95–97], the sea lily *Gymnocrinus richeri* [98], and tunicates *Ascidia nigra*, *Dendrogyra cylindrus* [88].

Two cytotoxic steroids, 5α,8α-epidioxycholesta-6,9(11),24-trien-3β-ol (34) and 5α,8α-epidioxycholesta-6,23-dien-3β,25-diol (35) were isolated from a marine sponge *Monanchora* sp. [99]. Series 5α,8α-epidioxy steroids: 20, 21, 23, 32, and 36–41 were isolated from the MeOH extracts of the Gorgonian *Eunicella cavolini* and the tunicate *Trididemnum inarmatum*. Compound (36), bearing a cyclopropyl moiety in the side chain, exhibited the highest antiproliferative activity [100]. Structures (36–41) can be seen in Figure 3, and their biological activity are presented in Table 3.
3. Polycyclic Endoperoxides Derived from Fungi and Fungal Endophytes

Fungi, fungal endophytes, myxomycetes, and the lichenized Ascomycetes are of great interest to pharmacologists and chemists, since they produce many biologically active substances, such as aromatic and phenolic compounds, tannins, hydrocarbons, lipids, unusual steroids, triterpenoids, heterocyclic compounds, peptides, and polycyclic endoperoxides [101–114].

Figure 3. Bioactive polycyclic endoperoxides derived from marine sources and fungi.
Table 3. Biological activity of natural polycyclic peroxides derived from marine sources and fungi.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|---------------------------------|-------------------------------------------|------------------------------------------|
| 36 | Antiprotozoal (Plasmodium) (0.884) | Antineoplastic (0.859) | Anti-inflammatory (0.881) |
|    | Apoptosis agonist (0.719)         |                            | Anti-fungal (0.644)                      |
| 37 | Antiprotozoal (Plasmodium) (0.816) | Antineoplastic (0.725) | Analgesic (0.812)                        |
|    | Antiparasitic (0.806)             |                            | Anti-fungal (0.745)                      |
| 38 | Antiprotozoal (Plasmodium) (0.789) | Antineoplastic (0.721) | Analgesic (0.806)                        |
|    | Antiparasitic (0.807)             |                            | Anti-fungal (0.730)                      |
| 39 | Antiprotozoal (Plasmodium) (0.765) | Antineoplastic (0.732) | Antileukemic (0.729)                     |
|    | Antiparasitic (0.763)             |                            | Anti-fungal (0.670)                      |
| 40 | Antiprotozoal (Plasmodium) (0.778) | Antineoplastic (0.726) | Antileukemic (0.717)                     |
|    | Antiparasitic (0.745)             |                            | Anti-fungal (0.669)                      |
| 41 | Antiparasitic (0.814)             | Antineoplastic (0.734) | Anti-helmintic (0.765)                   |
|    | Antiprotozoal (Plasmodium) (0.744) | Antimetastatic (0.625) | Anti-fungal (0.708)                      |
| 42 | Antiparasitic (0.863)             | Antineoplastic (0.799) | Anti-helmintic (0.731)                   |
|    | Antiprotozoal (Plasmodium) (0.716) | Antimetastatic (0.689) | Anti-fungal (0.705)                      |
| 43 | Antiprotozoal (Plasmodium) (0.882) | Antineoplastic (0.824) | Anti-inflammatory (0.821)                |
| 44 | Antiprotozoal (Plasmodium) (0.702) | Apoptosis agonist (0.910) | Anti-inflammatory (0.686) |
|    | Antineoplastic (0.782)             |                            | Antileukemic (0.659)                      |
| 45 | Antiprotozoal (Plasmodium) (0.898) | Antineoplastic (0.856) | Alzheimer’s disease treatment (0.732) |
| 46 | Antiprotozoal (Plasmodium) (0.775) | Antineoplastic (0.868) | Alzheimer’s disease treatment (0.698) |
| 47 | Antiprotozoal (Plasmodium) (0.844) | Antineoplastic (0.843) | Chemopreventive (0.712) |
|    | Chemopreventive (0.712)             |                            | Anti-fungal (0.659)                      |
| 48 | Antiprotozoal (Plasmodium) (0.835) | Antineoplastic (0.823) | Chemopreventive (0.679) |
|    | Chemopreventive (0.679)             |                            | Anti-fungal (0.662)                      |
| 49 | Antiprotozoal (Plasmodium) (0.829) | Antineoplastic (0.818) | Chemopreventive (0.644) |
|    | Chemopreventive (0.644)             |                            | Anti-leukemic (0.645)                     |
| 50 | Antiprotozoal (Plasmodium) (0.743) | Antineoplastic (0.788) | Anti-fungal (0.670)                      |
|    | Antimetastatic (0.603)             |                            | Anti-inflammatory (0.656)                |
| 51 | Antiprotozoal (Plasmodium) (0.752) | Antineoplastic (0.859) | Prostate cancer treatment (0.655) |
|    | Prostate cancer treatment (0.655) |                            | Anti-fungal (0.670)                      |
|    |                               |                            | Anti-inflammatory (0.661)                |
| 52 | Antiprotozoal (Plasmodium) (0.752) | Antineoplastic (0.859) | Analgesic (0.843)                        |

* Only activities with Pa > 0.5 are shown.

3. Polycyclic Endoperoxides Derived from Fungi and Fungal Endophytes

Fungi, fungal endophytes, myxomycetes, and the lichenized Ascomycetes are of great interest to pharmacologists and chemists, since they produce many biologically active substances, such as aromatic and phenolic compounds, tannins, hydrocarbons, lipids, unusual steroids, triterpenoids, heterocyclic compounds, peptides, and polycyclic endoperoxides [101–114].

In fungi, both cultivated and wild, polycyclic endoperoxides are found in small quantities, but ergosterol peroxide (33) is the most abundant [5,6]. Below, we present data on the distribution of this steroid and other polycyclic endoperoxides in fungi, fungal endophytes and lichens.

Trung and co-workers [115], using a modernized quantitative high-performance liquid chromatography method, found that ergosterol peroxide is present in wild mushrooms such as Fomitopsis dochiomus, F. carneus, Daldinia concentrica, Ganoderma applanatum, G. lobatum, G. multiplicder G. lucidum, Phellinus igniarius, and Trametes gibbosa. In addition, this
steroid has been detected in other species of wild fungi, fungal endophytes and lichens: *Claviceps purpurea*, *Ganoderma lucidum*, *G. tsugae*, *G. sichuanense*, *Daedaelea quercina*, *Pi toporus betulinus*, *Cryptotoporus volvatus*, *Guignardia laricina*, *Lampt eromyces japonicus*, *Botrytis cinerea*, *Lactarius culterius*, *L. volvens*, *Cryptotoporus volvatus*, *Dicty onema glabratum*, *Lasiosphaera nigro nica*, *Gloeophyllum odoratum*, *Gymnopilus speci tabilis*, *Herici um erinaceus*, *Hypszizigus marmoreus*, *Inonot us obliquus*, *I. radiatus*, *Lenzites betulina*, *Meripilus giganteus*, *Micro porus flabelliformis*, *Naematoloma fasciculare*, *Phellinus pini*, *P. ribis*, *P. torulosum*, *Roseoforms subflexibilis*, *Pyropoly porus fomentarius*, *Pisolithus tinctorius*, *Polyporus tuberaster*, *Pseudephebe pubescens* [5, 6, 17, 116], and from the edible mushroom *Volvariella volvacea* [117]. In addition, ergosterol peroxide has been found in some Ascomycetes, *Aspergillus* sp., *A. niger*, *A. oryzae*, *A. flavus*, *A. terreus*, and *A. fumigatus*, *Fusarium moniliforme*, *F. osyeporum*, *Penicillium rubrum*, and *P. sclercoti genum* [5]. Ragasa [118] researched Philippine mushrooms and found ergosterol peroxide in *Auricularia auricula-judae*, *Coprinopsis lagopus*, *Pleurotus florida*, and *Phellinus gibbus*.

It is known that ergosterol peroxide isolated from edible or medicinal mushrooms demonstrates antitumor activity against colorectal cancer, hepatocellular carcinoma, prostate cancer, myeloma, and leukemia [119–123], and it also possesses antioxidant, anti-inflammatory, and antiviral activities, as well as induce the apoptosis of cancer cells [124–128].

Endoperoxide (42), bearing a keto group at the 12 position, has been isolated from the fungus *Fusarium moniliforme* [129]. Endoperoxyl glycoside (43) was detected in ethanol extract of the fungus *Lactarius volvens*, which demonstrated anticancer activity [130, 131]. Ergosterol peroxide (33) and unusual steroid called aspervisin A (44) have been isolated from endophytic fungus of *Aspergillus versicolor* that was isolated from the seaweed *Sargassum thunbergii*. Both steroid antibiotics showed antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [132], and another steroid named fuscoporianol D (45) was found in a MeOH extract of in field-grown mycelia of *Inonotus obliquus* [133].

Several steroids containing a 5,9-position peroxide moiety have been isolated from some mushroom extracts. For example, endoperoxide (46) was found in *Boletus calopus* white mushroom [134], and steroid (47) produces by two fungi *Panellus serotinus* and *Lepista nuda* [135]. Two steroids named nigerasterols A and B (48 and 49) were isolated from the extracts of an endophytic fungus of *Aspergillus niger* MA-132, which was isolated from the mangrove plant *Avicennia marina* [136], and steroids (49–52) were found in *Buna shimeji* and *Pleurotus ostreatus* [137]. A rare chimegrane-type sesquiterpenes called steperoxides A (53), B (54), C (55), and D (56) have been isolated from the hydnoid fungus *Steccherinum ochraceum* [Phanerochaetaeae]. Compound (53) demonstrated anticancer properties, and compounds (54 and 57) showed significant antimicrobial activity against *Staphylococcus aureus* [138–141]. Structures (53–68) can be seen in Figure 3, and their biological activity are presented in Table 4.

Anti-tumor nor-sesquiterpen endoperoxides presented talaperoxide A (57), B (58), C (59), and D (60) were isolated from culture of fungi *Talaromyces* species HN21-3C, and from a mangrove endophytic fungus, *Talaromyces flavus* isolated from the mangrove plant *Sonneratia apetala* [142]. Isolated fungal metabolites demonstrated antineoplastic activity against MCF-7, MDA-MB-435, HepG2, HeLa, and PC-3 cancer cell lines [143, 144]. Semi-synthetic derivative (61) of the fungal derived natural product showed the antiparasitic and cytotoxic activity against *Trypanosoma brucei* and Hela cells, respectively [145]. Chimegrane endoperoxide named merulin C (62), were isolated from the culture broth extract of an endophytic fungus of *Xylocarpus granatum* [146].
Caryophyllene-derived meroterpenoids, called cytosporolides A (63), B (64), and C (65), which have a unique peroxylactone skeleton, were isolated from cultures of the fungus Cytospora sp. Obtained metabolites demonstrated significant antimicrobial activity against the Gram-positive bacteria Staphylococcus aureus and S. pneumonia [147].

Two unprecedented spiroketal endoperoxides named chloropupukeanolides A (66) and B (67) were isolated from an endophytic fungus Pestalotiopsis fici. Compound (66) showed significant anti-HIV-1 and cytotoxic effects [148].

It is known that natural hypocrellin is a dark red dye with photodynamic activity against several microorganisms was isolated from the fungus Hypocrella bambusae, and its photooxidation product called peroxyhypocrellin (68) has an anthracene endoperoxide arrangement within the perylene quinone structure [149]. Structures (42–68) can be seen in Figures 3 and 4, and their biological activity is presented in Tables 3 and 4.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|-------------------------------|---------------------------------------|----------------------------------------|
| 53 | Antiprotozoal (Plasmodium) (0.911) | Antineoplastic enhancer (0.825) | Antifungal (0.688) |
|    | Antiparasitic (0.643) | Antineoplastic (0.794) | Anti-inflammatory (0.661) |
| 54 | Antiprotozoal (Plasmodium) (0.916) | Antineoplastic (0.833) | Antifungal (0.676) |
|    | Antiparasitic (0.650) | Apoptosis agonist (0.710) | Anti-inflammatory (0.661) |
| 55 | Antiprotozoal (Plasmodium) (0.919) | | Antineoplastic (0.839) |
| 56 | Antiprotozoal (Plasmodium) (0.904) | Antineoplastic (0.814) | Antifungal (0.646) |
|    | Antiparasitic (0.649) | Apoptosis agonist (0.670) | Anti-inflammatory (0.589) |
| 57 | Antiprotozoal (Plasmodium) (0.913) | Antineoplastic (0.795) | Antifungal (0.688) |
|    | Apoptosis agonist (0.760) | Anti-inflammatory (0.612) |
| 58 | Antiprotozoal (Plasmodium) (0.902) | Antineoplastic enhancer (0.825) | Antifungal (0.646) |
|    | Antiparasitic (0.666) | Antineoplastic (0.794) | Anti-inflammatory (0.611) |
| 59 | Antiprotozoal (Plasmodium) (0.923) | Antineoplastic (0.865) | Antifungal (0.671) |
| 60 | Antiprotozoal (Plasmodium) (0.908) | Antineoplastic enhancer (0.816) | Antifungal (0.677) |
|    | Antiparasitic (0.652) | Antineoplastic (0.799) | Anti-inflammatory (0.622) |
| 61 | Antiprotozoal (Plasmodium) (0.920) | Antineoplastic (0.825) | Antifungal (0.721) |
| 62 | Antiprotozoal (Plasmodium) (0.935) | Antineoplastic (0.716) | Antifungal (0.709) |
|    | Antineoplastic (renal cancer) (0.598) | | |
| 63 | Antiprotozoal (Plasmodium) (0.839) | Antineoplastic (0.756) | Antifungal (0.705) |
|    | Antiparasitic (0.780) | Antineoplastic (renal cancer) (0.592) | | |
| 64 | Antiprotozoal (Plasmodium) (0.836) | Antineoplastic (0.758) | Antifungal (0.711) |
| 65 | Antiprotozoal (Plasmodium) (0.835) | Antineoplastic (0.756) | Antifungal (0.705) |
| 66 | Antiprotozoal (Plasmodium) (0.877) | Antineoplastic (0.848) | Antiviral (0.768) |
| 67 | Antiprotozoal (Plasmodium) (0.877) | Antineoplastic (0.848) | Antiviral (0.768) |
| 68 | Antiprotozoal (Plasmodium) (0.938) | Antineoplastic (0.912) | Anti-inflammatory (0.908) |

* Only activities with Pa > 0.5 are shown.
4. Polycyclic Endoperoxides Derived from Plants and Liverworts

The largest amount of endoperoxides has been found, isolated and partially biological activity determined in plants and liverworts [1,2,5,6,8,9,14,19,150–154].

A peroxide-sesquetepene, called nardosaldehyde (69) was isolated from the roots of Nardostachys chinensis, and biological activity was not determined [155]. Structures (69—89) can be seen in Figure 5, and their biological activity is presented in Tables 5 and 6. Peroxygibberol (16) is marine peroxide (5.9%) was also found in Agarwood oil obtained from highly infected Aquilaria malaccensis wood [156].

Figure 4. Bioactive polycyclic endoperoxides derived from fungi and fungal endophytes.
Figure 5. Bioactive polycyclic endoperoxides derived from plants.

An antimalarial guaiane-type sesquiterpenoids (70), nardoperoxide (71), and isonardoperoxide (72) were isolated from *Nardostachys chinensis* roots [157–159], and in addition to this, nardoguaianone A (73), B (74), C (75), and D (76) were also highlighted from the same plant [160].

Widdarol peroxide (77) and its analogue (78) were found in hexane extract from the fruits of *Schisandra grandiflora*, which showed anti-proliferative activity against Hela cancer cell lines [161].
Molecules 2021, 26, 686

(cervical cancer), A549 (lung cancer), DU-145 (prostate cancer), and MCF-7 (breast cancer) cancer cell lines [161].

Table 5. Biological activity of the natural polycyclic peroxides derived from plants.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|--------------------------------|------------------------------------------|------------------------------------------|
| 69 | Antiprotozoal (Plasmodium) (0.930) | Antineoplastic (0.674) | Phobic disorders treatment (0.604) |
|    | Antimetastatic (0.536) | | Ovulation inhibitor (0.550) |
| 70 | Antiprotozoal (Plasmodium) (0.756) | Antineoplastic (0.787) | Analgesic (0.883) |
|    | Antiparasitic (0.662) | Antimetastatic (0.591) | |
| 71 | Antiprotozoal (Plasmodium) (0.729) | Antineoplastic (0.788) | Analgesic (0.883) |
|    | Antiparasitic (0.662) | Antimetastatic (0.591) | Antileukemic (0.564) |
| 72 | Antiprotozoal (Plasmodium) (0.743) | Antineoplastic (0.769) | Analgesic (0.883) |
|    | Antimetastatic (0.591) | | Antileukemic (0.564) |
| 73 | Antiprotozoal (Plasmodium) (0.755) | Antineoplastic (0.801) | Analgesic (0.883) |
|    | Antiparasitic (0.662) | Antimetastatic (0.591) | Antileukemic (0.564) |
| 74 | Antiprotozoal (Plasmodium) (0.722) | Antineoplastic (0.855) | Analgesic (0.843) |
|    | Antiparasitic (0.510) | Prostate cancer treatment (0.641) | Anti-inflammatory (0.648) |
| 75 | Antiprotozoal (Plasmodium) (0.739) | Antineoplastic (0.855) | Analgesic (0.843) |
|    | Antiparasitic (0.510) | Prostate cancer treatment (0.641) | Antileukemic (0.513) |
|    | | Antimetastatic (0.517) | Antibacterial (0.503) |
| 76 | Antiprotozoal (Plasmodium) (0.964) | Apoptosis agonist (0.862) | Antifungal (0.538) |
|    | | Antineoplastic (0.694) | Antiviral (Arbovirus) (0.536) |
| 77 | Antiprotozoal (Plasmodium) (0.954) | Apoptosis agonist (0.910) | Atherosclerosis treatment (0.520) |
|    | Antiparasitic (0.553) | Antineoplastic (0.768) | |
|    | | Antimetastatic (0.587) | |
| 78 | Antiprotozoal (Plasmodium) (0.805) | Antineoplastic (0.949) | Anti-inflammatory (0.924) |
|    | Apoptosis agonist (0.797) | Antineoplastic (0.595) | Anti-fungal (0.703) |
|    | Antimetastatic (0.505) | | |
| 79 | Antiprotozoal (Plasmodium) (0.855) | Antineoplastic (0.582) | Immunosuppressant (0.706) |
| 80 | Antiprotozoal (Plasmodium) (0.900) | Antineoplastic (0.873) | Anti-psoriatic (0.630) |
| 81 | Antiprotozoal (Plasmodium) (0.964) | Antineoplastic (0.602) | Phobic disorders treatment (0.725) |

*Only activities with Pa > 0.5 are shown.

Polycyclic sesquiterpene, 1α,8α-epidioxy-4α-hydroxy-5αH-guai-7(11),9-dien-12,8-olide (79), which has anti-influenza viral properties, were isolated from the plant Curcuma wenyujin, which is mainly in the Wenzhou region of China [162] and was recently found in the flowering plant Acorus calamus [163]. Diterpenoid, (E,E)-15-hydroxylabda-8(17),11,13-trien-16-al (80) was detected in an extract of Alpinia chinensis [164]. Cadinane sesquiterpene, (−)-(5S,6S,7S,9R,10S)-7-hydroxy-5,7-epidioxycadinan-3-ene-2-one (81) was isolated and identified from the aerial part of the invasive plant Eupatorium adenophorum [165]. Diterpenoids called mulinic acid (82) and 17-acetoxymulinic acid (83) have been isolated from the aerial parts of Mulinum crassifolium (Umbelliferae) [166,167], and semi-synthetic derivatives (94, 95 and 96) were obtained from mulinic acid [168,169].

A cytotoxic seven-membered endoperoxide hemiacetal called coronarin B (84) was isolated from the flowers of Alpinia chinensis and Hedychium coronarium [164,170,171]. Unusual diterpene peroxide (85), with potent activity against Plasmodium falciparum, has been isolated from Anomum krervanh [172].
Table 6. Biological activity of the natural polycyclic peroxides derived from plants.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|--------------------------------|------------------------------------------|----------------------------------------|
| 82 | Antiprotozoal (Plasmodium) (0.868) | Antineoplastic (0.887) | Anti-inflammatory (0.946) |
| 83 | Antiprotozoal (Plasmodium) (0.809) | Antineoplastic (0.813) | Anti-inflammatory (0.898) |
| 84 | Antiprotozoal (Plasmodium) (0.882) | Apoptosis agonist (0.948) | Anti-inflammatory (0.867) |
| 85 | Antiprotozoal (Plasmodium) (0.912) | Antineoplastic (0.813) | Cardiotonic (0.939) |
| 86 | Antiprotozoal (Plasmodium) (0.996) | Apoptosis agonist (0.919) | Antifungal (Candida) (0.915) |
| 87 | Antiprotozoal (Leishmania) (0.966) | Apoptosis agonist (0.847) | Anti-schistosome (0.961) |
| 88 | Antiprotozoal (Toxoplasma) (0.918) | DNA synthesis inhibitor (0.644) | Antifungal (Cryptococcus) (0.955) |
| 89 | Antiparasitic (0.883) | DNA synthesis inhibitor (0.590) | Anti-schistosome (0.975) |
| 90 | Antiprotozoal (Coccidia) (0.794) | | Antifungal (Aspergillus) (0.627) |
| 91 | Antiprotozoal (Plasmodium) (0.966) | Apoptosis agonist (0.890) | Antifungal (Candida) (0.976) |
| 92 | Antiprotozoal (Leishmania) (0.949) | Apoptosis agonist (0.820) | Anti-schistosome (0.970) |
| 93 | Antiprotozoal (Toxoplasma) (0.928) | DNA synthesis inhibitor (0.545) | Antifungal (Aspergillus) (0.950) |
| 94 | Antiparasitic (0.880) | | Anti-schistosome (0.832) |
| 95 | Antiprotozoal (Coccidia) (0.792) | Apoptosis agonist (0.787) | Antifungal (Aspergillus) (0.761) |
| 96 | Antiprotozoal (Plasmodium) (0.982) | Apoptosis agonist (0.755) | Anti-schistosome (0.915) |
| 97 | Antiprotozoal (Leishmania) (0.966) | DNA synthesis inhibitor (0.592) | Anti-schistosome (0.849) |
| 98 | Antiprotozoal (Toxoplasma) (0.875) | Apoptosis agonist (0.884) | Antifungal (Candida) (0.942) |
| 99 | Antiparasitic (0.876) | Antineoplastic (0.828) | Anti-schistosome (0.868) |
| 100 | Antiprotozoal (Coccidia) (0.649) | DNA synthesis inhibitor (0.607) | Antifungal (Cryptococcus) (0.825) |
| 101 | Antiprotozoal (Plasmodium) (0.990) | Apoptosis agonist (0.884) | Antifungal (Aspergillus) (0.607) |
| 102 | Antiprotozoal (Leishmania) (0.929) | Antineoplastic (0.828) | Antifungal (Aspergillus) (0.631) |
| 103 | Antiprotozoal (Toxoplasma) (0.899) | DNA synthesis inhibitor (0.607) | Antiviral (CMV) (0.603) |
| 104 | Antiparasitic (0.886) | Antineoplastic (0.838) | Anti-schistosome (0.960) |
| 105 | Antiprotozoal (Coccidia) (0.689) | Prostate disorders treatment (0.675) | Anti-schistosome (0.942) |
| 106 | Antiprotozoal (Plasmodium) (0.860) | Antineoplastic (0.838) | Anti-inflammatory (0.819) |
| 107 | Antiparasitic (0.768) | Cardiovascular analeptic (0.733) | Anti-psoriatic (0.690) |

* Only activities with Pa > 0.5 are shown.

Endoperoxide called artemisinin (86) was found in 1979 in the extract of the Chinese herb qinghaosu (Artemisia annua) [173]. Currently, artemisinin and its derivatives (87–93) are widely used throughout the world as antimalarial drugs against the protozoan parasites [174–177]. An interesting mechanism of action for these compounds appears to
involve heme-mediated degradation of the endoperoxide bridge to form carbon-centered free radicals, and these free radicals are selectively toxic to malaria parasites [178–180]. Artemisinin and its derivatives exhibit antitumor, antifungal, and other activities [181–183]. Structures (90–114) can be seen in Figure 6, and their biological activity is presented in Tables 6 and 7.

Table 7. Biological activity of natural polycyclic peroxides derived from plants.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|-----------------------------|------------------------------------------|------------------------------------------|
| 94 | Antiprotozoal (Plasmodium) (0.868) | Antineoplastic (0.887) | Anti-inflammatory (0.946) |
| 95 | Antiprotozoal (Plasmodium) (0.874) | Antineoplastic (0.870) | Anti-inflammatory (0.941) |
| 96 | Antiprotozoal (Plasmodium) (0.889) | Antineoplastic (0.769) | Anti-inflammatory (0.918) |
| 97 | Antiprotozoal (Plasmodium) (0.936) | Antineoplastic (0.932) | Anti-inflammatory (0.958) |
|    | Apoptosis agonist (0.617) | | Antifungal (Candida) (0.630) |
| 98 | Antiprotozoal (Plasmodium) (0.936) | Antineoplastic (0.932) | Anti-inflammatory (0.958) |
|    | Apoptosis agonist (0.617) | | Antifungal (Candida) (0.630) |
| 99 | Antiprotozoal (Plasmodium) (0.928) | Antineoplastic (0.681) | Anti-inflammatory (0.544) |
| 100| Antiprotozoal (Plasmodium) (0.916) | Antineoplastic (0.854) | Anti-inflammatory (0.945) |
| 101| Antiprotozoal (Plasmodium) (0.879) | Antineoplastic (0.866) | Anti-inflammatory (0.934) |
|    | Antiparasitic (0.649) | Antimetastatic (0.623) | Anti-helminthic (0.609) |
| 102| Antiprotozoal (Plasmodium) (0.965) | Antineoplastic (0.792) | Carminative (0.652) |
|    | Antiparasitic (0.576) | Antimetastatic (0.584) | |
| 103| Antiprotozoal (Plasmodium) (0.954) | Apoptosis agonist (0.565) | Carminative (0.832) |
| 104| Antiprotozoal (Plasmodium) (0.956) | Antineoplastic (0.670) | Anti-eczematic (0.700) |
|    | Antiparasitic (0.574) | Antimetastatic (0.587) | Anti-helminthic (0.593) |
| 105| Antiprotozoal (Plasmodium) (0.959) | Antineoplastic (0.678) | Anti-eczematic (0.711) |
|    | Antiparasitic (0.581) | Antimetastatic (0.588) | Anti-helminthic (0.599) |
| 106| Antiprotozoal (Plasmodium) (0.938) | Antineoplastic (sarcoma) (0.734) | Carminative (0.812) |
| 107| Antiprotozoal (Plasmodium) (0.945) | Antineoplastic (sarcoma) (0.529) | Anti-eczematic (0.715) |
| 108| Antiprotozoal (Plasmodium) (0.881) | Antineoplastic (0.699) | Anti-eczematic (0.734) |
| 109| Antiprotozoal (Plasmodium) (0.884) | Antineoplastic (0.862) | Anti-eczematic (0.861) |
|    | Antiparasitic (0.672) | Apoptosis agonist (0.795) | Anti-inflammatory (0.679) |
| 110| Antiprotozoal (Plasmodium) (0.967) | Antineoplastic (0.911) | Anti-eczematic (0.836) |
|    | Antiparasitic (0.811) | Apoptosis agonist (0.883) | Anti-fungal (0.812) |
|    | Antiprotein (Leishmania) (0.731) | DNA synthesis inhibitor (0.652) | Antibacterial (0.667) |
| 111| Antiprotozoal (Plasmodium) (0.889) | Antineoplastic (0.769) | Angiogenesis stimulant (0.644) |
| 112| Antiprotozoal (Plasmodium) (0.917) | Antineoplastic (0.797) | Carminative (0.724) |
|    | Prostate cancer treatment (0.650) | | Anti-inflammatory (0.697) |
| 113| Antiprotozoal (Plasmodium) (0.752) | Antineoplastic (0.946) | Anti-inflammatory (0.949) |
| 114| Antiprotozoal (Plasmodium) (0.925) | Antineoplastic (0.914) | Anti-eczematic (0.851) |
|    | Antiparasitic (0.741) | | Anti-helminthic (0.702) |

* Only activities with Pa > 0.5 are shown.
Endoperoxyl cuparene-type sesquiterpenoids (97 and 98, structures are shown in Figure 6, and activity is shown in Table 7) were identified from the Japanese liverwort Jungermannia infusca [184,185]. The chamigranes called merulin B (99) and C (100) have been found in an extract of the culture broth of a Thai mangrove-derived fungus [186,187].

Muurolane sesquiterpene endoperoxide, 1,4-peroxy-5-hydroxy-muurol-6-ene (101) has been obtained from plant Illicium tsangii (family Schisandraceae) [188–190]. The peroxide called schisansphene A (102) was isolated from the plant Schisandra sphenanthera, also known as the magnolia berry [191].

Figure 6. Bioactive polycyclic endoperoxides derived from plants and liverworts.
Highly oxygenated sesquiterpene (+)-muurolan-4,7-peroxide (103) was found in the essential oil of the liverwort Plagiochila asplenioides [192], and two sesquiterpene endoperoxides (104 and 105) were isolated from the aerial parts of the invasive plant Eupatorium adenophorum [193,194]. Unusual endoperoxide (106) was detected in the Ligularia veitchiana [195], compound (107) was isolated from the leaves of Eupatorium adenophorum [196], and metabolite (108) was found in extracts of the Xylopia emarginata [197]. The aerial parts of Montanoa hibiscifolia afforded rare endoperoxide (109) [198].

The xanthane-type sesquiterpenoid 4β,5β-epoxyxanthatin-1α,4α-endoperoxide (110) was found in the aerial parts of Xanthium strumarium [199], and 2α,5α-endoperoxide (111), which possess the 6α,12-eudesmanolide structure, was detected in aerial parts of the Artemisia herba-alba [200]. The sesquiterpene peroxide (112) has been found from the aerial parts of Croton arboreous [201].

Allohimachalane peroxide (113) has been obtained from Illicium tsangii [188–190], and an unusual sesquiterpene lactone with endoperoxide group, called tehranolide (114) with strong antimalarial activity has been discovered in many Iranian Artemisia species: A. aucheri, A. austriaca, A. biennis, A. campestris, A. deserti, A. diffusa, A. gypsacea, A. haussknechtii, A. kermanshensis, A. kopetdaghensis, A. kulbadica, A. oliveriana, A. persica, A. santolina, A. sieberi, A. tschernieviana, A. ciniformis, A. incana, A. turanica, and A. tournefortiana [202].

The hemiacetal of tricycloperoxyhumulone A (115) was detected in hops (Humulus lupulus) [203]. Structures (115–128) can be seen in Figure 7, and their biological activity is presented in Table 8. Highly oxygenated limonoid featuring an unprecedented 3,4-peroxide-bridged A-seco skeleton called walsuronoid A (116) was isolated from Walsura robusta (family Meliaceae). The isolated peroxide showed weak antimalarial activity [204].

### Table 8. Biological activity of natural polycyclic peroxides derived from plants.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|-------------------------------|------------------------------------------|----------------------------------------|
| 115 | Antiprotozoal (Plasmodium) (0.920) | Antineoplastic (0.719) | Allergic conjunctivitis treatment (0.597) |
| 116 | Antiprotozoal (Plasmodium) (0.904) | Antineoplastic (0.752) | Anti-inflammatory (0.815) |
| 117 | Antiprotozoal (Plasmodium) (0.886) | Antineoplastic (0.899) | Antifungal (0.807) |
| 118 | Antiprotozoal (Plasmodium) (0.891) | Antineoplastic (0.902) | Anti-inflammatory (0.854) |
| 119 | Antiprotozoal (Plasmodium) (0.877) | Antineoplastic (0.904) | Anti-inflammatory (0.836) |
| 120 | Antiprotozoal (Plasmodium) (0.878) | Antineoplastic (0.879) | Anti-inflammatory (0.823) |
| 121 | Antiprotozoal (Plasmodium) (0.734) | Antineoplastic (0.828) | Anti-inflammatory (0.807) |
| 122 | Antiprotozoal (Plasmodium) (0.955) | Antineoplastic (0.783) | Anti-inflammatory (0.731) |
| 123 | Antiprotozoal (Plasmodium) (0.702) | Antineoplastic (0.762) | Lipid metabolism regulator (0.617) |
| 124 | Antiprotozoal (Plasmodium) (0.869) | Antineoplastic (0.853) | Anti-inflammatory (0.869) |
| 125 | Antiprotozoal (Leishmania) (0.582) | Antineoplastic (0.804) | Anti-inflammatory (0.807) |
| 126 | Antiprotozoal (Plasmodium) (0.848) | Antineoplastic (0.821) | Anti-inflammatory (0.899) |
Table 8. Cont.

| No  | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|-----|--------------------------------|------------------------------------------|------------------------------------------|
| 126 | Antiprotozoal (Plasmodium) (0.835) | Apoptosis agonist (0.919) | Anti-inflammatory (0.858) |
|     |                               | Antineoplastic (0.842)                     | Diuretic (0.748)                          |
| 127 | Antiprotozoal (Plasmodium) (0.891) | Antineoplastic (0.874)                     | Hepatoprotectant (0.838)                  |
|     |                               | Apoptosis agonist (0.871)                  | Antifungal (0.716)                        |
| 128 | Antiprotozoal (Plasmodium) (0.891) | Antineoplastic (0.874)                     | Hepatoprotectant (0.838)                  |
|     |                               | Apoptosis agonist (0.871)                  | Antifungal (0.716)                        |

* Only activities with Pa > 0.5 are shown.

Figure 7. Bioactive polycyclic endoperoxides derived from plants.
A cytotoxic peroxytriterpene dilactone called pseudolarolide I (117) has been isolated from the seeds of *Pseudolarix kaempferi* [205], and the leaves of *P. kaempferi* contain three triterpene peroxides, pseudolarolides Q (118), R (119), and S (120) [206]. An unusual glycoside, 3β,15α,25-trihydroxy-16,23-dioxo-6α,19α-epidioxy-9,10-seco-9,19-cyclolanost-5(10),9(11)-dien 3-O-α-L-arabinopyranoside called podocarpaside E (121), was isolated from the roots of *Actaea podocarpa* [207].

A triterpene, 5α,6α-epidioxy-5β,6β-epoxy-9,13-dimethyl-25,26-dinoroleanan-3β-ol acetate, called aceranol acetate (122), which shows anti-inflammatory activity, was isolated from the stems and leaves of *Acer mandshuricum* [208]. The isolated compound also exhibited moderate activity against four human cancer cell lines (HL-60, SK-OV-3, A549, and HT-29).

A peroxy-multiflorane triterpene ester, (3α,5α,8α,20α)-5,8-epidioxymultiflora-6,9(11)-dien-3,29-diol 3,29-dibenzoate (123), was isolated from the processed seeds of *Trichosanthes kirilowii*. The obtained compound showed in vitro cytotoxicity against human-tumor cell lines (Hela, HL-60, and MCF-7) [209]. A peroxy triterpene, 3β-acetoxy-1β,11α-epidioxy-12-ursene (124), was isolated from the aerial roots of *Ficus microcarpa* [210]. An antimicrobial triterpenoid, 1α,5α-dioxy-11α-hydroxyurs-12-en-3-one (125), was found and obtained from the rhizome of *Vladimiria multiflora* [211].

The benzene extract of the bark of *Sapium baccatum* contained the nor-triterpene peroxide baccatin (126), which has been isolated and studied [212]. Two highly oxygenated ursane-type triterpenoids, (2β,3β)-3,25-epidioxy-2,24-dihydroxyursa-12,20(30)-dien-28-oic acid (127) and (2β,3β)-3,25-epidioxy-2,24-dihydroxyurs-12-en-28-oic acid (128), were detected in the EtOH extract of *Gentiana aristata* [213].

Highly oxygenated steroidal metabolites called physalin K (129) and Q (130) were found in extracts of the aerial parts of *Physalis alkekengi* var. *franchetii* [214]. Structures (129–143) can be seen in Figure 8, and their biological activity is presented in Table 9. Plant withanolide called jaborosalaracacetone 15 (131) was isolated from the flowering plant *Jaborosa odonelliana*, which was collected during autumn in Argentina [215]. Physangulidin G (132) was isolated from the aerial parts of *Deprea bitteriana*, *D. cuyacensis*, and *D. zamorae* [216].

Table 9. Biological activity of natural polycyclic peroxides derived from plants.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|--------------------------------|------------------------------------------|----------------------------------------|
| 129 | Antiprotozoal (0.969) Antineoplastic (0.812) Immunosuppressant (0.586) |
| 130 | Antiprotozoal (Plasmodium) (0.966) Antimetastatic (0.504) Antifungal (0.521) |
| 131 | Antiprotozoal (0.967) Antineoplastic (0.819) Antibacterial (0.657) |
| 132 | Antiprotozoal (Plasmodium) (0.837) Antineoplastic (0.788) Antifungal (0.609) |
| 133 | Antiprotozoal (Plasmodium) (0.846) Apoptosis agonist (0.934) Prostate cancer treatment (0.636) Hypolipemic (0.820) Anti-hypercholesterolemic (0.608) Atherosclerosis treatment (0.679) |
| 134 | Antiprotozoal (Plasmodium) (0.894) Antineoplastic (0.875) Antifungal (0.703) |
| 135 | Antiprotozoal (Plasmodium) (0.952) Antineoplastic (0.756) Anti-eczematic (0.863) |
| 136 | Antiprotozoal (Plasmodium) (0.782) Antineoplastic (0.879) Antineoplastic (sarcoma) (0.671) Anti-inflammatory (0.681) |
| 137 | Antiprotozoal (Plasmodium) (0.908) Antineoplastic (0.833) Antifungal (0.714) |
Table 9. Cont.

| No | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|----|--------------------------------|------------------------------------------|------------------------------------------|
| 138 | Antiprotozoal (Plasmodium) (0.970) Antiparasitic (0.867) | Apoptosis agonist (0.920) Antineoplastic (0.850) DNA synthesis inhibitor (0.687) | Antifungal (Candida) (0.908) Antifungal (Cryptococcus) (0.844) Antifungal (0.812) |
| 139 | Antiprotozoal (Plasmodium) (0.972) Antiparasitic (0.864) | Apoptosis agonist (0.938) DNA synthesis inhibitor (0.754) | Antifungal (Candida) (0.903) Antifungal (0.833) |
| 140 | Antiprotozoal (Plasmodium) (0.977) | Antineoplastic (0.914) DNA synthesis inhibitor (0.733) | Antifungal (Candida) (0.899) Antifungal (0.834) |
| 141 | Antiprotozoal (Plasmodium) (0.894) | Antineoplastic (0.943) | Anti-inflammatory (0.883) |
| 142 | Antiprotozoal (Plasmodium) (0.983) Antiparasitic (0.868) | Apoptosis agonist (0.955) Antineoplastic (0.841) DNA synthesis inhibitor (0.712) | Antifungal (0.858) Antibacterial (0.633) |
| 143 | Antiprotozoal (Plasmodium) (0.988) Antiparasitic (0.859) | Apoptosis agonist (0.950) Antineoplastic (0.848) DNA synthesis inhibitor (0.718) | Antifungal (0.860) Antibacterial (0.635) |

* Only activities with Pa > 0.5 are shown.

Figure 8. Bioactive polycyclic endoperoxides derived from plants.
A unique compound, a 3,9-(1,2,3-trioxocine)-type steroid called rauianodox (133), and an ergosterol peroxide (33) were isolated from the Australian plant *Rauia nodosa* (family Rutaceae) [217]. An unusual endoperoxide called schinalactone A (134), which has a compressed ring A and shows anticancer activity against PANC-1 cell lines, was detected in the stems and roots of the magnolia vine, *Schisandra sphenanthera* [218].

A secoadianane-type steroid (135) was found and identified in the herbaceous plant *Dorstenia brasiliensis* (Moraceae) [219,220]. A polycyclic peroxide called vielanin D (136), which showed anti-plasmodial activity, was extracted from fresh and dry leaves of the plant *Senecio selloi* [221]. The peroxy steroid (16S,23R)-16,23-epoxy-23,25-epidioxycycloartan-3-one (137) was found in the Texas yellow-star, *Lindheimera texana* (Asteraceae) [222].

Two triterpenes, called gilvanol (138) and 3-deoxydilvanol (139), have been detected in the extracts of the red-bark oak, *Quercus gilva* [170,223]. An interesting endoperoxide, adian-5-ene ozonide (140) was found in the fern leaves of *Adiantum monochlamys* (Pteridaceae) and *Oleandra wallichii* (Davalliaceae), and another peroxide, a triterpene ozonide (141), was detected in the root extract of *Senecio selloi* [224,225].

Interesting and rare 1,2,4-trioxolanes (142 and 143) were derived from natural two allobetulin derivatives; however, biological activity has not been determined [226]. Two 9,13-diepoxy labdane diterpenoids called amoenolide K (144) and its 19-acetate (145) were detected in the areal parts from *Amphiachyris amoena* [227], and ent-8β,12α-epidioxy-12β-hydroxylabda-9(11),13-dien-15-oic acid γ-lactone (146) was obtained from the aerial parts of *Premna oligotricha* [228]. Structures (144–154) can be seen in Figure 9, and their biological activity is presented in Table 10.

![Figure 9](image-url)
Table 10. Biological activity of natural polycyclic peroxides derived from plants.

| No  | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|-----|--------------------------------|-------------------------------------------|----------------------------------------|
| 144 | Antiprotozoal (Plasmodium) (0.900) | Antineoplastic (0.873) | Respiratory analeptic (0.635) |
|     |                                | Apoptosis agonist (0.850)                   | Anti-psoriatic (0.630)               |
| 145 | Antiprotozoal (Plasmodium) (0.893) | Antineoplastic (0.873) | Respiratory analeptic (0.642) |
|     |                                | Apoptosis agonist (0.852)                   | Anti-psoriatic (0.639)               |
| 146 | Antiprotozoal (Plasmodium) (0.846) | Antineoplastic (0.857) | Anti-psoriatic (0.685)               |
| 147 | Antiprotozoal (Plasmodium) (0.888) | Antineoplastic (0.824) | Chemopreventive (0.675) |
|     |                                | Apoptosis agonist (0.750)                   | Choleretic (0.545)                   |
|     | Antiprotozoal (Plasmodium) (0.734) | Antineoplastic (0.798) | Anti-psoriatic (0.639)               |
| 148 |                                | Antiparasitic (0.544)                        | Anti-psoriatic (0.532)               |
| 149 | Antiprotozoal (Plasmodium) (0.801) | Antineoplastic (0.871) | Prostate disorders treatment (0.627) |
| 150 | Antiprotozoal (Plasmodium) (0.915) | Antineoplastic (0.848) | Antibacterial (0.647)                |
| 151 | Antiprotozoal (Plasmodium) (0.772) | Antineoplastic (0.726) | Antileukemic (0.602)                 |
| 152 | Antiprotozoal (Plasmodium) (0.829) | Antineoplastic (0.685) | Anti-eczematic (0.794)               |
| 153 | Antiprotozoal (Plasmodium) (0.905) | Antineoplastic (0.805) | Carminative (0.505)                  |
|     | Antiparasitic (0.727)            |                                          | Anti-psoriatic (0.504)               |
| 154 | Antiprotozoal (Plasmodium) (0.854) | Antineoplastic (0.804) | Antimitotic (0.597)                  |
|     |                                |                                          | Antifungal (0.553)                   |

* Only activities with Pa > 0.5 are shown.

Diterpenic acids (13, 14, 147 and 148) have been identified from lipid extract of the different species. The diterpenic acid methyl ester (147) was isolated from the leaves of Moroccan Juniperus thurifera and J. phoenicea [229], compound (148) was detected in MeOH extract of Saffia oxyodon [230], and two abietic acids (13 and 14) were obtained from aerial parts from the Abies marocana, Lepechinia caulescens, and Caryopteris nepetaefolia [231–233].

The diterpenoid endoperoxide called EBC-325 (149) was obtained from an extract of Croton insularis [234,235]. The diterpenoid endoperoxide called jungermatrobrunin A (150), detected in the liverwort Jungermannia atrobrunnea, has an unusual rearrangement-kaurene skeleton with a peroxide bridge [236], and two similar oxygenated diterpenes called triptotins A (151) and B (152) were found in extracts of the Tripterygium wilfordii [237]. The roots of Jatropha curcas contained peroxide caniojane (153) [238], and another peroxide called steenkroton B (154) was found in ethanol extract of the leaves of Croton steenkampianus (Euphorbiaceae), which displayed mild anti-plasmodial activity [239].

Several adamantane type polycyclic polyprenylated acylphloroglucinols (155–164) possessing an unprecedented seco-adamantane architecture combined with a peroxide ring have been isolated and identified from extracts of some plants [240]. Thus, one compound called hypersubone B (155) was isolated from the leaves of Hypericum subsessile and exhibited significant cytotoxicity against four human cancer lines in vitro, HepG2, Eca109, HeLa, and A549 [241], and hyperisampsins N (157) and O (158), which exhibited significant cytotoxic activities toward HL-60 cells, were found in the aerial parts of H. sampsonii [242]. Structures (155–164) can be seen in Figure 10, and their biological activity is presented in Table 11.
Table 11. Biological activity of natural polycyclic peroxides derived from plants.

| No  | Antiprotozoal Activity, (Pa) * | Anticancer and Related Activities, (Pa) * | Additional Biological Activities, (Pa) * |
|-----|---------------------------------|------------------------------------------|----------------------------------------|
| 155 | Antiprotozoal (Plasmodium) (0.861) | Antineoplastic (0.788)                   | Antioxidant (0.551)                     |
|     | Antiparasitic (0.503)            | Apoptosis agonist (0.784)                | Antibacterial (0.505)                   |
|     |                                 | Chemopreventive (0.521)                 |                                        |
| 156 | Antiprotozoal (Plasmodium) (0.862) | Antineoplastic (0.767)                   | Hypolipemic (0.581)                     |
|     |                                 | Apoptosis agonist (0.744)               |                                        |
| 157 | Antiprotozoal (Plasmodium) (0.874) | Antineoplastic (0.761)                   | Antiviral (Arbovirus) (0.579)           |
|     |                                 | Apoptosis agonist (0.743)               |                                        |
| 158 | Antiprotozoal (Plasmodium) (0.875) | Antineoplastic (0.735)                   |                                        |
|     |                                 | Apoptosis agonist (0.675)               |                                        |
| 159 | Antiprotozoal (Plasmodium) (0.861) | Antineoplastic (0.788)                   | Antioxidant (0.551)                     |
|     | Antiparasitic (0.503)            | Apoptosis agonist (0.784)                | Antibacterial (0.505)                   |
|     |                                 | Chemopreventive (0.521)                 |                                        |
| 160 | Antiprotozoal (Plasmodium) (0.875) | Antineoplastic (0.735)                   |                                        |
|     |                                 | Apoptosis agonist (0.675)               |                                        |
| 161 | Antiprotozoal (Plasmodium) (0.874) | Antineoplastic (0.761)                   | Antiviral (Arbovirus) (0.579)           |
|     |                                 | Apoptosis agonist (0.743)               |                                        |
| 162 | Antiprotozoal (Plasmodium) (0.811) | Apoptosis agonist (0.892)                | Antioxidant (0.657)                     |
|     |                                 | Antineoplastic (0.710)                  |                                        |
| 163 | Antiparasitic (0.798)            | Antineoplastic (0.958)                   |                                        |
|     | Antiprotozoal (Plasmodium) (0.731) | Apoptosis agonist (0.630)               |                                        |
|     | Antiprotozoal (Leishmania) (0.557) | Cytostatic (0.576)                      |                                        |
|     |                                 |                                         |                                        |
| 164 | Antiparasitic (0.779)            | Antineoplastic (0.960)                   |                                        |
|     | Antiprotozoal (Plasmodium) (0.744) | Proliferative diseases treatment (0.740) |                                        |
|     |                                 | Chemopreventive (0.666)                 |                                        |
|     |                                 | Apoptosis agonist (0.627)               |                                        |
| 165 | Antiparasitic (0.771)            | Antineoplastic (0.963)                   |                                        |
|     | Antiprotozoal (Plasmodium) (0.737) | Proliferative diseases treatment (0.742) |                                        |
|     |                                 | Chemopreventive (0.656)                 |                                        |
|     |                                 | Apoptosis agonist (0.629)               |                                        |
| 166 | Antiparasitic (0.798)            | Antineoplastic (0.959)                   |                                        |
|     | Antiprotozoal (Plasmodium) (0.732) | Anticarcinogenic (0.732)               |                                        |
|     |                                 | Chemopreventive (0.731)                 |                                        |
|     |                                 | Apoptosis agonist (0.622)               |                                        |
| 167 | Antiparasitic (0.813)            | Antineoplastic (0.960)                   |                                        |
|     | Antiprotozoal (Plasmodium) (0.728) | Chemopreventive (0.740)               |                                        |
|     |                                 | Apoptosis agonist (0.631)               |                                        |
| 168 | Antiparasitic (0.843)            | Antineoplastic (0.962)                   |                                        |
|     | Antiprotozoal (Plasmodium) (0.771) | Proliferative diseases treatment (0.834) |                                        |
|     |                                 | Apoptosis agonist (0.666)               |                                        |
|     |                                 | Antimetastatic (0.517)                  |                                        |
| 169 | Antiprotozoal (Plasmodium) (0.874) | Antineoplastic (0.761)                   | Antiviral (Arbovirus) (0.579)           |
|     |                                 | Apoptosis agonist (0.743)               |                                        |
| 170 | Antiprotozoal (Plasmodium) (0.875) | Antineoplastic (0.735)                   |                                        |
|     |                                 | Apoptosis agonist (0.675)               |                                        |
| 171 | Antiprotozoal (Plasmodium) (0.861) | Antineoplastic (0.788)                   |                                        |
|     | Antiparasitic (0.503)            | Apoptosis agonist (0.784)                |                                        |
|     |                                 | Chemopreventive (0.521)                 |                                        |

* Only activities with Pa > 0.5 are shown.
Figure 10. Bioactive adamantane type polycyclic endoperoxides derived from plants.

Peroxsampsones A and B (156 and 162) were isolated from the roots of the Chinese medicinal plant *H. sampsonii*, and compound (156) showed comparable activity with norfloxacin against a NorA over-expressing multidrug-resistant strain of *Staphylococcus aureus* SA-1199B [243]. Two prenylated benzophenone derivatives, plukenetiones C (159) and hydroperoxide (160), have been isolated from the fruits of the Barbadian plant *Clusia plukenetii* [244], and otogirinin B (98) was detected in *Hypericum erectum* [245]. Garcimultiflorone G (163), which shows anti-inflammatory activity, was isolated from the fruits of *Garcinia multiflora* [246], and another polycyclic peroxide called goianone (164) was found in fruits extracts of *Clusia rosea* [247].

Unusual polycyclic endoperoxides pregnane glycosides named periplocosides A (165), B (166) C (167), D (168), K (169), F (170), and E (171) have been isolated from the antitumor fraction, which was obtained from the CHCl₃ extract of *Periploca sepium* [248–250]. Structures (165–171) can be seen in Figure 11, and their biological activity is presented in Table 11.
5. Comparison of Biological Activities of Natural Polycyclic Endoperoxides

It is currently accepted that the biological activity of both natural and synthetic compounds depends on their structure [33,251,252]. Despite the activity cliffs observed for some drug-like compounds [253], which can be considered as a violation of this rule,
structure-activity relationships (SAR) are widely used in medicinal chemistry for finding and optimization new pharmacological agents [254].

PASS is the first software for in silico estimation of biological activity profiles [33,255], of which the development has been started more than 30 years ago [256]. Its current implementation predicts about 8000 pharmacological effects, molecular mechanisms of action, pharmacological effects, toxicity, side effects, anti-targets, transporters-related interactions, gene expression regulation, and metabolic terms [31]. Due to the utilization of chemical descriptors that reflect the essential features of ligand-target interactions and a robust mathematical approach for analysis of structure-activity relationships, the average accuracy of PASS predictions was 96% [31,252,257,258]. Based on the PASS predictions provided by the appropriate web-service [259], over 29,000 researchers from 104 countries selected the most promising virtually designed molecules for synthesis and determined the optimal directions for testing their biological activity [260–264].

In this study, PASS predictions were used to estimate the general pharmacological potential for the analyzed natural polycyclic endoperoxides. For about 8000 pharmacological effects and molecular mechanisms of action, probabilities of belonging to the class of “actives” Pa, varied from zero to one, were estimated. The higher the Pa value is, the higher the probability of confirming the predicted activity in the experiment. On the other hand, estimated Pa values might be relatively small for some activities if the analyzed molecule is not like the active compounds from the PASS training set. Thus, PASS prediction interpretation requires considering two contradictory issues high probability of activity vs. high structural novelty. The researcher decides which issue is more critical, depending on the task or the project [18,31,35,257,258].

5.1. Antiprotozoal Activity of Natural Polycyclic Endoperoxides

Currently, about 120,000 articles have been published that are devoted to antiprotozoal and antiparasitic activities of both natural and synthetic compounds [265–271].

Analyzing the data obtained with PASS of natural polycyclic endoperoxides and artemisinin and its analogs currently used in medicine, it can be stated that for all polycyclic endoperoxides, antiprotozoal activity is estimated with a Pa from 70 to 99.6%. For some compounds, antiparasitic activity is also estimated, with a Pa from 50 to 88.3%. The antiprotozoal and antiparasitic activities predicted using the PASS are shown in Tables 1–11, and the chemical structures are shown in Figures 1–11. A 3D graph of the predicted pharmacological activities of artemisinin (86) and its analogs is shown in Figure 12.

Artemisinin and its analogs (both natural and synthetic) are widely used in medical practice and are essential antimalarial treatment components. Figure 12 shows the predicted pharmacological activities of artemisinin and its analogs using PASS, and Figure 13 demonstrates the predicted pharmacological activities of artemisinin.

5.2. Antitumor and Other Activities of Natural Polycyclic Endoperoxides

Many natural products exhibit antitumor and related activities and belong to different classes of chemical compounds, such as alkaloids, aromatic and phenolic metabolites, lipids, glycosides, and compounds containing acetylene or epoxy moieties [272–278]. These compounds also refer to various types of terpenoids, including steroids, triterpenoids, carotenoids, and polycyclic endoperoxides.

More than one million articles and reviews have been devoted to various antitumor and related activities of both natural and synthetic compounds. In an earlier section, we presented and discussed the antitumor activity of polycyclic endoperoxides isolated from various terrestrial and aquatic organisms computed using PASS.

According to the PASS estimates presented in Tables 1–11, many endoperoxides demonstrate antitumor and related activities to varying degrees. However, we are interested in compounds for which such activity is estimated with more than 95% probability. Figure 14 demonstrates natural compounds and their predicted antitumor activity with Pa > 95%.
Figure 12. The 3D graph shows the predicted and calculated pharmacological activities of artemisinin (86) and its analogs, such as 12α-OH-artemisinin (87), 12β-OH-artemisinin (88), artemether (89), arteether (90), artelinate (91), and artesunic acid (92). According to the PASS data, artemisinin and its analogs (86–92) show selective activity against obligate intracellular protozoan parasites belonging to the genera Plasmodium, Toxoplasma, Leishmania, and Coccidia, which is the main pharmacological activity with a confidence level of more than 90%. In addition, all these endoperoxides show antifungal activity against the opportunistic pathogenic yeasts Candida and Cryptococcus, as well as anticancer activity for some compounds; the confidence level exceeds 90 percent.

Figure 13. The 3D graph shows the predicted and calculated pharmacological activities of artemisinin (86), which was found in 1979 in the extract of the Chinese herb Qinghaosu (Artemisia annua). According to PASS data, this endoperoxide demonstrated 16 different activities, with 5 activities having a found confidence of more than 90 percent. Antiprotozoal selective activity of artemisinin against obligate intracellular protozoan parasites belonging to the genera Plasmodium (99.5%), Toxoplasma (93%), Leishmania (92.3%), and Coccidia (78%) is the main pharmacological activity. In addition, artemisinin demonstrated strong anti-schistosomal activity (91.1%) against Schistosoma mansoni, a human blood fluke parasite. Additionally, artemisinin shows antifungal activity against an opportunistic pathogenic yeast Candida (91.5%) and Cryptococcus (85.3%), although anticancer activity is found at 80%.
Figure 14. The 3D graph shows the predicted and calculated antitumor activity of selected polycyclic endoperoxides (compound numbers: 11, 17, 30, 33, 142, 143, 164, and 165) showing the highest degree of confidence, more than 95%. These polycyclic endoperoxides can be used in clinical medicine as agents with strong antitumor activity.

Some polycyclic endoperoxides, in addition to antiparasitic, antiprotozoal, and antitumor activities, demonstrate other activities with Pa > 90%, which should also be mentioned in this article. This is primarily anti-inflammatory activity. Figure 15 demonstrates such compounds as well as their predicted anti-inflammatory activity. It should also be noted that endoperoxide artemisinin (86) and its analogs, and some other compounds, show antifungal activity. Figure 16 demonstrates predicted antifungal activity with Pa > 90%.

Figure 15. The 3D graph shows the predicted and calculated anti-inflammatory activity of selected polycyclic endoperoxides (compound numbers: 1, 8, 9, 68, 94, 95, 96, 97, 98, 100, and 113) showing the highest degree of confidence, i.e., more than 95%. These polycyclic endoperoxides can be used as potential agents with strong anti-inflammatory activity.
Figure 15. The 3D graph shows the predicted and calculated anti-inflammatory activity of selected polycyclic endoperoxides (compound numbers: 1, 8, 9, 68, 94, 95, 96, 97, 98, and 113) showing the highest degree of confidence, i.e., more than 95%. These polycyclic endoperoxides can be used as potential agents with strong anti-inflammatory activity.

Figure 16. The 3D graph shows the predicted and calculated antifungal activity of selected polycyclic endoperoxides (compound numbers: 86, 87, 88, 89, 90, 91, 92, 138, and 139) polycyclic endoperoxides showing the highest degree of confidence, more than 95%.

6. Conclusions

In this review, we presented more than 170 polycyclic endoperoxides isolated from various sources and showed that all endoperoxides demonstrate antiprotozoal activity with varying degrees of reliability, and among them, the artemisinin group and some other compounds are significantly distinguished from all endoperoxides presented and have a strong antiprotozoal activity. Our data only confirm that the artemisinin group has unique properties, which is why it has been used in medical practice for more than 50 years in the fight against malaria parasites. In addition, the artemisinin group has a high antifungal activity, while some other endoperoxides have a strictly strong anti-inflammatory activity.

Compounds such as (19), (23), and (25) exhibited anti-hypercholesterolemic action, and compounds (166) and (168) have a strong stimulating effect on the respiratory and vasomotor centers of the brain. However, to confirm the conclusions regarding the in silico estimations, more research is required.

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References
1. Dembitsky, V.M. Bioactive peroxides as potential therapeutic agents. Eur. J. Med. Chem. 2008, 43, 223–251. [CrossRef] [PubMed]
2. Dembitsky, V.M.; Gloriozova, T.A.; Poroikov, V.V. Natural peroxy anticancer agents. Mini Rev. Med. Chem. 2007, 7, 571–589. [CrossRef] [PubMed]
3. Dembitsky, V.M. Oxidation, epoxidation and sulfoxidation reactions catalysed by haloperoxidases. Tetrahedron 2003, 26, 4701–4720. [CrossRef]
4. Dembitsky, V.M. Chemistry and biodiversity of the biologically active natural glycosides. Chem. Biodivers 2004, 1, 673–781. [CrossRef] [PubMed]

5. Casteel, D.A. Peroxy natural products. Nat. Prod. Rep. 1992, 9, 289–312. [CrossRef]

6. Casteel, D.A. Peroxy natural products. Nat. Prod. Rep. 1999, 16, 55–73. [CrossRef]

7. Siddiq, A.; Yaremenko, I.; Terent’v, A.O.; Gloriozova, T.A.; Dzemileva, L.U.; D’yakonov, A.V.; Vil, V.; Dembitsky, V.M. Phytomedicinal aspects of sesquiterpenoid peroxides: Origin, structures and biological activity. Frontiers Drug Chem. Clin. Res. 2019, 2, 1–10.

8. Sikorsky, T.V.; Ermolenko, E.V.; Gloriozova, T.A.; Dembitsky, V.M. Mini Review: Anticancer activity of diterpenoid peroxides. Vietnam J. Chem. 2020, 58, 278–280. [CrossRef]

9. Dembitsky, V.M.; Yaremenko, I.A. Stable and unstable 1,2-dioxolanes: Origin, synthesis, and biological activities. Sci. Synth. Knowl. Updates 2020, 38, 277–321.

10. Dembitsky, V.M.; Vil, V.A. Medicinal chemistry of stable and unstable 1,2-dioxetanes: Origin, formation, and biological activities. Sci. Synth. Knowl. Updates 2019, 38, 333–377.

11. Noronha, M.; Pawar, V.; Pratapati, A.; Subramanian, R.B. A literature review on traditional herbal medicines for malaria. S. Afr. J. Bot. 2020, 128, 292–303. [CrossRef]

12. Bu, M.; Yang, B.B.; Hu, L. Natural endoperoxides as drug lead compounds. Curr. Med. Chem. 2016, 23, 383–405. [CrossRef] [PubMed]

13. Vil, V.A.; Gloriozova, T.A.; Poroikov, V.V.; Terent’ev, A.O.; Savidov, N.; Dembitsky, V.M. Peroxy steroids derived from plant and fungi and their biological activities. Appl. Microbiol. Biotechnol. 2018, 102, 7657–7667. [CrossRef] [PubMed]

14. Vil, V.A.; Terent’ev, A.O.; Savidov, N.; Gloriozova, T.A.; Poroikov, V.V.; Pounina, T.A.; Dembitsky, V.M. Hydroperoxy steroids and triterpenoids derived from plant and fungi: Origin, structures and biological activities. J. Steroid Biochem. Mol. Biol. 2019, 190, 76–87. [CrossRef] [PubMed]

15. Dembitsky, V.M.; Poovarodom, S.; Leontowicz, H.; Leontowicz, M.; Vearasilp, S.; Trakhtenberg, S.; Gorinstein, S. The multiple nutrition properties of some exotic fruits: Biological activity and active metabolites. Food Res. Intern. 2011, 44, 1671–1701. [CrossRef]

16. Dembitsky, V.; Shkrob, I.; Hanus, L.O. Ascaridole and related peroxides from the genus Chenopodium. Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub. 2008, 152, 209–215. [CrossRef]

17. Dembitsky, V.M. Astonishing diversity of natural peroxides as potential therapeutic agents. J. Mol. Genet. Med. 2015, 9, 100163.

18. Ermolenko, E.V.; Imbs, A.B.; Gloriozova, T.A.; Poroikov, V.V.; Sikorskaya, T.V.; Dembitsky, V.M. Chemical diversity of soft coral steroids and their pharmacological activities. Mar. Drugs 2020, 18, 613. [CrossRef]

19. Dembitsky, V.M. Antitumor and hepatoprotective activity of natural and synthetic neo steroids. Prog. Lipid Res. 2020, 79, 101048. [CrossRef]

20. Mayer, A.M.S.; Guerrero, A.J.; Rodriguez, A.D.; Taglialetela-Scafati, O.; Nakamura, F.; Fusetani, N. Marine pharmacology in 2014–2015: Marine compounds with antibacterial, anti-diabetic, anti-fungal, anti-inflammatory, anti-protozoal, antituberculosis, antiviral, and anthelmintic activities; Affecting the immune and nervous systems, and other miscellaneous mechanisms of action. Mar. Drugs 2020, 18, 5.

21. Bude, S.; Goerdeler, F.; Floß, J.; Kreitmeier, P.; Hicks, E.F.; Moscovitz, O.; Seeberger, P.H.; Davies, H.M.L.; Reiser, O. Visible light mediated oxidative ring expansion of annelated cyclopropanes to fused endoperoxides with antimalarial activity. Org. Chem. Front. 2020, 7, 1789–1795. [CrossRef]

22. Yang, J.; He, Y.; Li, Y.; Zhang, X.; Wong, Y.K.; Shen, S.; Zhong, T.; Zhang, J.; Liu, Q.; Wang, J. Advances in the research on the targets of anti-malaria actions of artemisinin. Pharmacol. Ther. 2020, 216, 106979. [CrossRef] [PubMed]

23. Tadjudeen, N.; Van Heerden, F.R. Anti-plasmodial natural products: An update. Malar. J. 2019, 18, 404. [CrossRef] [PubMed]

24. Rukunga, G.; Simons, A. The Potential of Plants as a Source of Antimalarial Agents: A Review; Planta Philae Publications: Berlin, Germany, 2006; 72p.

25. Tiwari, M.K.; Chaudhary, S. Artemisinin-derived antimalarial endoperoxides from bench-side to bed-side: Chronological advancements and future challenges. Med. Res. Rev. 2020, 40, 1220–1275. [CrossRef] [PubMed]

26. Kotepeu, M.; Kotepeu, K.U.; Milanex, G.D. Global prevalence and mortality of severe Plasmodium malariae infection: A systematic review and meta-analysis. Malar. J. 2020, 19, 274. [CrossRef] [PubMed]

27. Sharp, P.M.; Penderleith, L.J.; Hahn, B.H. Ape Origins of human malaria. Annu. Rev. Microbiol. 2020, 74, 39–63. [CrossRef] [PubMed]

28. Enserink, M. Malaria researchers wait for industry to join fight. Science 2000, 287, 1956–1958. [CrossRef] [PubMed]

29. Chima, R.I.; Goodman, C.A.; Mills, A. The economic impact of malaria in Africa: A critical review of the evidence. Health Policy 2003, 63, 17–36. [CrossRef]

30. Cock, J.E.; Selesho, M.I.; van Vuuren, S.F. A review of the traditional use of southern African medicinal plants for the treatment of malaria. J. Ethnopharm. 2019, 245, 112176. [CrossRef]

31. Poroikov, V.V. Computer-aided drug design: From discovery of novel pharmaceutical agents to systems pharmacology. Biochem. (Moscow) Suppl. Ser. B Biomed. Chem. 2020, 14, 216–227. [CrossRef]
64. Dembisky, V.M.; Rozentsvet, O.A. Phospholipid composition of some marine red algae. _Phytochemistry_ **1990**, 29, 3149–3152. [CrossRef]

65. Butler, M.S.; Capon, R.J. Trunculin-F and contrunculin-A and -B: Novel oxygenated norterpenes from a southern Australian marine sponge, _Latrunculia conula_. _Aust. J. Chem._ **1993**, 46, 1363–1374. [CrossRef]

66. Ovenden, S.P.; Capon, R.J. Trunculins G–I: New norterpenete cyclic peroxides from a southern Australian marine sponge, _Latrunculia sp._ _Aust. J. Chem._ **1998**, 51, 573–580. [CrossRef]

67. Hirade, H.; de Voogd, N.J.; Suzuki, T.; Tanaka, J. Trunculins X and Y from an Okinawan sponge _Signosceptrella sp._ _Tetrahedron_ **2019**, 75, 4620–4625. [CrossRef]

68. Gonzalez, A.G.; Martin, J.D.; Perez, C.; Rovirosa, J.; Tagle, B.; Clardy, J. Isolation and X-ray structural determination of three new diterpenoids from the marine alga _Taonia atomaria_. _Chem. Lett._ **1984**, 13, 1649–1652. [CrossRef]

69. Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, I. Absolute configurations of cytotoxic marine cembranolides; Consideration of mosher’s method. _Tetrahedron Lett._ **1979**, 29, 4731–4734. [CrossRef]

70. Uchio, Y.; Eguchi, S.; Kuramoto, J.; Nakayama, M.; Hase, T. Denticulatolide, an ichthyotoxic peroxide-containing cembranolide from the soft coral _Lobophytum denticulatum_. _Tetrahedron Lett._ **1985**, 26, 4487–4490. [CrossRef]

71. Fukazawa, Y. Conformational study of the cembranolide diterpene denticulatolide by molecular mechanics method. _Tetrahedron Lett._ **1986**, 27, 1825–1828. [CrossRef]

72. Uchio, Y.; Shizuko, E.; Yoshimasa, F.; Mitsuaki, K. 7-Epidenticulatolide, a new cembranolide with a cyclic peroxide function from _Sigmosceptrella sp._ _Tetrahedron_ **1989**, 45, 1397–1399. [CrossRef]

73. Hirota, H.; Okino, T.; Yoshimura, E.; Fusetani, N. Five new antifouling sesquiterpenes from two marine sponges of the genus _Aplysilla pallida_. _Tetrahedron Lett._ **1990**, 31, 1047–1049. [CrossRef]

74. Monaco, P.; Pallini, M.; Preveritera, L. Two endoperoxide diterpenes from _Elodea canadensis_. _Tetrahedron Lett._ **1987**, 28, 4609–4612. [CrossRef]

75. Hirota, H.; Okino, T.; Yoshimura, E.; Fusetani, N. Five new antifouling sesquiterpenes from two marine sponges of the genus _Axinysa_ and the nudibranch _Phyllidia pustulosa_. _Tetrahedron_ **1998**, 54, 13971–13980. [CrossRef]

76. Ahmed, A.F.; Kuo, Y.-H.; Dai, C.-F.; Sheu, J.H. Oxygenated terpenoids from a Formosan Soft coral _Sinularia gibberosa_. _J. Nat. Prod._ **2005**, 68, 1208–1212. [CrossRef]

77. Sera, Y.; Adachi, K.; Shizuri, Y. A new epidioxy sterol as an antifouling substance from a _Palythoa_ marine sponge. _J. Nat. Prod._ **1997**, 50, 903–910. [CrossRef]

78. Seo, Y.W.; Rho, J.R.; Cho, K.W.; Sim, C.J.; Shin, J.H. Isolation of epidioxysteroids from _Aplysilla pallida_. _Aust. J. Chem._ **1997**, 50, 903–910. [CrossRef]

79. Seo, Y.; Rho, J.R.; Shin, J. Isolation of two steroids from the marine polychaete worm _Perinereis_ _abhiwata_. _Ocean Res._ **1998**, 18, 83–87. [CrossRef]

80. Fattorussio, E.; Magni, S.; Santacroce, C.; Sica, D. Sterol peroxides from the sponge _Axinella cannabina_. _Gazz. Chim. Gazz._ **1974**, 104, 409–413. [CrossRef]

81. Gauvin, A.; Smadja, J.; Aknin, M.; Faure, R.; Gaydou, E.M. 5α,8α-Epideoxycholest-6-en-3-β-ol from the marine sponge _Haplosclerida_ _Odontella aurita_. _Can. J. Chem._ **1998**, 76, 986–992. [CrossRef]

82. Ahmed, A.F.; Kuo, Y.-H.; Dai, C.-F.; Sheu, J.H. Oxygenated terpenoids from _Pathosma_ _Soft coral_ _Sinularia gibberosa_. _J. Nat. Prod._ **2005**, 68, 1208–1212. [CrossRef]

83. Abouriche, A.; Charron, M.; Chaib, N.; Bennamar, A.; Bontemps, N.; Francisco, C. Isolation and bioactivities of epidioxysteroids from the sponge _Cynthia_ _savinigyi_. _Furmarc._ **2000**, 55, 492–494. [CrossRef]

84. Minh, C.V.; Van Kiem, P.; Kim, Y.H. Cytotoxic constituents of _Diadema setosum_. _Arch. Pharmacal. Res._ **2004**, 27, 734–737. [CrossRef]

85. Gunatilaka, A.A.L.; Gopichand, Y.; Schmitz, F.J.; Djerrassi, C. Minor and trace sterols in marine invertebrates. 26. Isolation and structure elucidation of nine new 5α,8α-epideoxy sterols from four marine organisms. _J. Org. Chem._ **1981**, 46, 3860–3866. [CrossRef]

86. Jimenez, C.; Quio, A.E.; De Caste, L.; Riguera, R. Epideoxy sterols from the tunicates _Dendrodoa grossularia_ and _Ascidia aspersa_ and the gastropoda _Aplysia depilans_ and _Aplysia punctate_. _J. Nat. Prod._ **1986**, 49, 905–909. [CrossRef]

87. Findlay, J.A.; Patil, A.D. A novel steroid peroxide from the sea anemone _Metridium senile_. _Steroids_ **1984**, 44, 261–265. [CrossRef]

88. Sheikh, Y.M.; Djerrassi, C. Steroids from sponges. _Tetrahedron_ **1974**, 30, 4095–4103. [CrossRef]

89. Anjaneyulu, A.S.R.; Sagar, K.S.; Venugopal, M.J.R.V. Terpenoid and steroid constituents of the Indian ocean soft coral _Sinularia maxima_. _Tetrahedron_ **1995**, 51, 10997–11010. [CrossRef]

90. Faulkner, D.J. Marine natural products. _Nat. Prod. Rep._ **1997**, 14, 257–302. [CrossRef]

91. Faulkner, D.J. Marine natural products. _Nat. Prod. Rep._ **1991**, 8, 97–114. [CrossRef]

92. Toume, K.; Ishibashi, M. 5α,8α-Epideoxycholesterol sulfate from a diatom _Odontella aurita_. _Phytochemistry_ **2002**, 61, 359–360. [CrossRef]

93. Yaoita, Y.; Amemiya, K.; Ohnuma, H.; Furumura, K.; Masaki, A.; Matsuki, T.; Kikuchi, M. Sterol constituents from five edible mushrooms. _Chem. Pharm. Bull._ **1998**, 46, 944–950. [CrossRef]

94. Stonard, R.J.; Petrovich, J.C.; Andersen, R.J. A new C26 sterol peroxide from the opisthobranch mollusk _Adalaria_ _sp._ and the sea pen _Virgularia_ _sp._ _Steroids_ **1980**, 36, 81–86. [CrossRef]
95. Prawat, H.; Mahidol, C.; Wittayalai, S.; Intachote, P.; Kanchanapoom, T.; Ruchirawat, S. Nitrogenous sesquiterpenes from the Thai marine sponge Halichondria sp. Tetrahedron 2011, 67, 5651–5655. [CrossRef]

96. Mishra, P.D.; Wahidullah, S.; De Souza, L.; Kamat, S.Y. Lipid constituents of marine sponge Suberites carnosus. Indian J. Chem. 1996, 35, 806–809.

97. Im, K.S.; Nam, K.I.; Sim, C.J.; Jung, J.H. Sterol peroxide derivatives from the marine sponge Spirastrella abata. Korean J. Pharmacog. 2000, 31, 401–406.

98. Feng, Y.; Khokhara, S.; Davis, R.A. Crinoids: Ancient organisms, modern chemistry. Nat. Prod. Rep. 2017, 34, 571–584. [CrossRef]

99. Mun, B.; Wang, W.; Kim, H. Cytotoxic α,β-epidioxy sterols from the marine sponge Monanchora sp. Arch. Pharm. Res. 2015, 38, 18–25. [CrossRef]

100. Ioannou, E.; Aazika, A.F.A.; Dimitrios, M.Z.; Xanthippi, C.; Constantinos, A.; Alexisd, V.M.N.; Roussisa, V. 5-

101. Dembitsky, V.M. The multiple properties of some of the lichenized Ascomycetes: Biological activity and active metabolites. In Plant Adaptation Strategies in Changing Environment; Shukla, V., Kumar, S., Kumar, N., Eds.; Springer: Singapore, 2017.

102. Torres, A.; Hochberg, M.; Pergament, I.; Smoum, R.; Niddam, V.; Dembitsky, V.M. A new UV-B absorbing mycosporine with photo protective activity from the lichenized ascomycete Collema cristatum. Eur. J. Biochem. 2004, 271, 780–784. [CrossRef]

103. Dembitsky, V.M.; Rezanka, T.; Spižek, J.; Hanuš, L.O. Secondary metabolites of slime molds (myxomycetes). Phytochemistry 2005, 66, 747–769. [CrossRef]

104. Dembitsky, V.M. Lipids of lichens. Prog. Lipid Res. 1992, 31, 373–397. [CrossRef]

105. Dembitsky, V.M.; Rezanka, T.; Bychek, I.A.; Shustov, M.V. Identification of fatty acids from Cladonia lichens. Phytochemistry 1991, 30, 4015–4018. [CrossRef]

106. Dembitsky, V.M.; Rezanka, T.; Bychek, I.A.; Shustov, M.V. Fatty acid composition of Parmelia lichens. Phytochemistry 1992, 31, 841–843. [CrossRef]

107. Dembitsky, V.M.; Rezanka, T.; Bychek, I.A.; Shustov, M.V. Fatty acids and phospholipids from lichens of the order Lecanorales. Phytochemistry 1992, 31, 851–853. [CrossRef]

108. Dembitsky, V.M.; Shubina, E.E.; Kashin, A.G. Phospholipid and fatty acid composition of some Basidiomycetes. Phytochemistry 1992, 31, 845–849. [CrossRef]

109. Dembitsky, V.M.; Terent’ev, A.O.; Levitsky, D.O. Amino and fatty acids of wild edible mushrooms of the genus Boletus. Records Nat. Prod. 2010, 4, 218–225.

110. Rustamova, N.; Bozorov, K.; Efferth, T. Novel secondary metabolites from endophytic fungi: Synthesis and biological properties. Phytochem. Rev. 2020, 19, 425–448. [CrossRef]

111. Vil, V.; Gloriozova, T.A.; Poroikov, V.V.; Terent’ev, A.O.; Savidov, N.; Dembitsky, V.M. Naturally occurring of α,β-diepoxy-containing compounds: Origin, structures, and biological activities. Appl. Microbiol. Biotech. 2019, 103, 3249–3264. [CrossRef]

112. Zhang, Y.; Han, T.; Ming, Q.; Wu, L.; Rahman, K.; Qin, L. Alkaloids produced by endophytic fungi: A review. Nat. Prod. Commun. 2012, 7, 963–968. [CrossRef]

113. Zhao, M.; Godecke, T.; Gunn, J.; Duan, J.A.; Che, C.T. Protostane and fusidane triterpenes: A mini review. Molecules 2013, 18, 4054–4080. [CrossRef] [PubMed]

114. Savidov, N.; Gloriozova, T.A.; Poroikov, V.V.; Dembitsky, V.M. Highly oxygenated isoprenoid lipids derived from fungi and fungal endophytes: Origin and biological activities. Steroids 2018, 140, 114–124. [CrossRef] [PubMed]

115. Trung, H.V.; Tuan, N.N.; Thanh, N.T.; Giang, T.T.B.; Giang, D.T.T.; Ogunwande, I.; Thang, T.D. Determination of ergosterol and ergosterol peroxide in higher fungi species by high-performance liquid chromatography. J. Pharm. Phytochem. 2018, 7, 2376–2379.

116. Dembitsky, V.M.; Rezanka, T.; Shubina, E.E. Unusual hydroxy fatty acids from some higher fungi. Phytochemistry 1993, 34, 1057–1059. [CrossRef]

117. Mallavadhani, U.U.; Sudhakar, A.V.S.; Satyanarayana, K.V.S.; Mahapatraa, A.; Li, W. Chemical and analytical screening of some edible mushrooms. Food. Chem. 2006, 95, 58–64. [CrossRef]

118. Ragasa, C.Y. Anticancer compounds from nine commercially grown and wild Philippine mushrooms. Manila J. Sci. 2018, 11, 42–57.

119. Kahlos, K.; Kangas, L.; Hiltunen, R. Ergosterol peroxide, an active compound from Inonotus radiatus. Planta Med. 1989, 55, 389–390. [CrossRef]

120. Chen, Y.K.; Kuo, Y.H.; Chiang, B.H.; Lo, J.M.; Sheen, L.Y. Cytotoxic activities of 9,11-dehydroergosterol peroxide and ergosterol peroxide from the fermentation mycelia of Ganoderma lucidum cultivated in the medium containing leguminous plants on Hep 3B cells. J. Agric. Food Chem. 2009, 57, 5713–5719. [CrossRef]

121. Kobori, M.; Yoshida, M.; Ohnishi-Kameyama, M.; Shinmoto, H. Ergosterol peroxide from an edible mushroom suppresses inflammatory responses in RAW264.7 macrophages and growth of HT29 colon adenocarcinoma cells. Br. J. Pharmacol. 2007, 150, 209–219. [CrossRef]

122. Russo, A.; Cardile, V.; Piovan, M.; Caggia, S.; Espinoza, C.L.; Garbarino, J.A. Pro-apoptotic activity of ergosterol peroxide and (22E)-ergosta-7,22-dien-5α-hydroxy-3,6-dione in human prostate cancer cells. Chem. Biol. Interact. 2010, 184, 352–358. [CrossRef]
123. Li, X.; Wu, Q.; Bu, M.; Hu, L.; Du, W.W.; Jiao, C.; Pan, H.; Sdiri, M.; Wu, N.; Xie, Y. Ergosterol peroxide activates Foxo3-mediated cell death signaling by inhibiting AKT and c-Myc in human hepatocellular carcinoma cells. *Oncotarget* **2016**, *7*, 33948–33959. [CrossRef] [PubMed]

124. Yasukawa, K.; Aoki, T.; Takido, M.; Ikekawa, T.; Saito, H.; Matsuzawa, T. Inhibitory effects of ergosterol isolated from the edible mushroom *Hypholoma marmoreum* on TPA-induced inflammatory ear oedema and tumour promotion in mice. *Phytother. Res.* **1994**, *8*, 10–13. [CrossRef]

125. Bu, M.; Cao, T.; Li, H.; Guo, M.; Yang, B.B.; Zeng, C.; Hu, L. Synthesis of 5α,8α-ergosterol peroxide 3-carbamate derivatives and a fluorescent mitochondria-targeting conjugate for enhanced antitumor activities. *ChemMedChem* **2017**, *12*, 466–474. [CrossRef] [PubMed]

126. Bu, M.; Cao, T.; Li, H.; Guo, M.; Yang, B.B.; Zeng, C.; Zhou, Y.; Zhang, N.; Hu, L. Synthesis and biological evaluation of novel steroidal 5α,8α-epidioxyandrost-6-ene-3β-ol-17-(O-phenylacetamide)oxime derivatives as potential anticancer agents. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3856–3861. [CrossRef]

127. Bok, J.W.; Lermer, L.; Chilton, J.; Klingeman, H.G.; Towers, G.H. Antitumor sterols from the mycelia of *Cordyceps sinensis*. *Phytochemistry* **1999**, *51*, 891–898. [CrossRef]

128. Govindharaj, M.; Arumugam, S.; Nirmala, G.; Bharadwaj, M.; Murugiyana, K. Effect of marine basidiomycetes fulviformes sp.-derived ergosterol peroxide on cytotoxicity and apoptosis induction in MCF-7 Cell Line. *J. Fungi* **2019**, *5*, 16. [CrossRef]

129. Serebryakov, E.P.; Simolin, A.V.; Kucherov, V.F.; Rosynov, B.V. New metabolites of Fusarium moniliforme shed. *Tetrahedron* **1970**, *26*, 5251–5219. [CrossRef]

130. Zang, M.; Ying, J.Z. *Economic fungi in the South West of China*; Scientific Press: Beijing, China, 1994.

131. Yue, J.M.; Chen, S.N.; Lin, Z.W.; Sun, H.D. Sterols from the fungus *Lactarium volemus*. *Phytochemistry* **2001**, *56*, 801–806. [CrossRef]

132. Miao, F.P.; Li, X.D.; Liu, X.H.; Cichewicz, R.H.; Ji, N.Y. Secondary metabolites from an algicolous *Aspergillus versicolor* strain. *Molecules* **2021**, *26*, 1–9. [CrossRef]

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

134. Zuo, W.; Luo, D.Q. Research on the chemical components of the fruit bodies of *Boletus calopus*. *Anhui Nongye Xuebao* **2010**, *38*, 2356–2357.

135. Yaoita, Y.; Matsuki, K.; Iijima, T.; Nakano, S.; Kakuda, R.; Machida, K.; Kikuchi, M. New sterols and terpenoids from four edible mushrooms. *Chem. Pharm. Bull.* **2001**, *49*, 589–594. [CrossRef] [PubMed]

136. Liu, D.; Li, X.M.; Li, C.S.; Wang, B.G. Nigerasterols A and B, antiproliferative sterols from the mangrovederived endophytic fungus *Aspergillus niger* MA-123. *Helv. Chim. Acta* **2013**, *96*, 1055–1061. [CrossRef]

137. Yaoita, Y.; Endo, K.; Tani, Y.; Machida, K.; Amemiya, K. Sterol constituents from seven mushrooms. *Chem. Pharm. Bull.* **1999**, *47*, 847–851. [CrossRef]

138. Liu, D.Z.; Luo, M.H. Two new chamigrane metabolites from fermentation broth of *Stecccherinum ochraceum*. *Fitoterapia* **2010**, *81*, 1205–1207. [CrossRef]

139. Liu, D.Z.; Dong, Z.J.; Wang, F.; Liu, J.K. Two novel norsesquiterpene peroxides from basidiomycete *Stecccherinum ochraceum*. *Tetrahedron Lett.* **2010**, *51*, 3152–3153. [CrossRef]

140. Li, L.B.; Ren, J.; Lai, R.; Cheng, Z.M.; Zhu, H.J. Natural cyclic peroxide echinobiophithene A with antimicrobial activity from *Echinops ritro*. *J. Chem. Chinese Univ.* **2011**, *32*, 891–896. [CrossRef]

141. Rahaman, M.S.; Siraj, M.A.; Sultana, S.; Seidel, V.; Islam, M.A. Molecular phylogenetics and biological potential of fungal *Echinops ritro*. *Tetrahedron* **2010**, *73*, 1880–1885. [CrossRef]

142. Li, H.; Huang, H.; Shao, C.; Huang, H.; Jiang, J. Cytotoxic norsesquiterpene peroxides from the endophytic fungus *Talaromyces flavus* isolated from the mangrove plant *Sonneratia apetala*. *Front. Microbiol.* **2015**, *6*, 33948–33959. [CrossRef] [PubMed]

143. She, Z.; Li, H.; Li, M.; Zhu, X.; Lin, Y. Norsesquiterpene Peroxide with Antitumor Activity and Preparation and Application Thereof. Chinese Patent CN 2011-10031487, 27 December 2011. Faming Zhuanli Shenqing.

144. Li, X.; Wu, Q.; Bu, M.; Hu, L.; Du, W.W.; Jiao, C.; Pan, H.; Sdiri, M.; Wu, N.; Xie, Y. Ergosterol peroxide activates Foxo3-mediated cell death signaling by inhibiting AKT and c-Myc in human hepatocellular carcinoma cells. *Oncotarget* **2016**, *7*, 33948–33959. [CrossRef] [PubMed]

145. Shao, C.; Huang, H.; Jiang, J. Cytotoxic norsesquiterpene peroxides from the endophytic fungus *Talaromyces flavus* isolated from the mangrove plant *Sonneratia apetala*. *Front. Microbiol.* **2015**, *6*, 33948–33959. [CrossRef] [PubMed]

146. Chen, W.-S.; Chen, Y.-T.; Wan, X.-Y.; Edmund, F.; Puff, H. Breitmaier, E. Die Struktur des Hypocrellins und seines Photooxidation-sproduktes Peroxyhypocrellin. *Liebigs Ann. Chem.* **1981**, *10*, 1880–1885.

147. Chen, W.-S.; Chen, Y.-T.; Wan, X.-Y.; Edmund, F.; Puff, H. Breitmaier, E. Die Struktur des Hypocrellins und seines Photooxidation-sproduktes Peroxyhypocrellin. *Liebigs Ann. Chem.* **1981**, *10*, 1880–1885.
182. Wong, Y.K.; Xu, C.; Kalesh, K.A.; He, Y.; Lin, Q.; Wong, W.S.F.; Shen, H.M.; Wang, J. Artemisinin as an anticancer drug: Recent advances in target profiling and mechanisms of action. Med. Res. Rev. 2017, 37, 1–26. [CrossRef]

183. Bhattacharjee, M.K. Antifungals, antimalarials, and antivirals. Chem. Antibiot. Relat. Drugs 2016, 12, 175–195.

184. Nagashima, F.; Suzuki, M.; Takaoka, S.; Asakawa, Y. New sesqui- and diterpenoids from the Japanese liverwort Jungermannia infusca (Mitt.) Sterh. Chem. Pharm. Bull. 1998, 46, 1184–1191. [CrossRef]

185. Nagashima, F.; Suzuki, M.; Takaoka, S.; Asakawa, Y. New acorane- and cuparane-type sesqui- and new labdane- and seco-labdane-type diterpenoids from the Japanese liverwort Jungermannia infusca (Mitt.) Steph. Tetrahedron 1999, 55, 9117–9121. [CrossRef]

186. Zhou, T.; Zhang, H.; Zhu, N.; Chiu, P. New triterpene peroxides from Pseudolarix kaempferi. [CrossRef]

187. Chokpaiboon, S.; Sommit, D.; Bunyapaiboonsri, T; Matsubara, K.; Pudhom, K. Antiangiogenic effect of chamigrane endoperoxides from a Thai mangrove-derived fungus. J. Nat. Prod. 2011, 74, 2290–2299. [CrossRef]

188. Chen, H.J.; Wu, Y. Expedient entry to the chamigane endoperoxide family of natural products. Org. Lett. 2015, 17, 592–595. [CrossRef] [PubMed]

189. Ngo, K.S.; Brown, G.D. Santalane and isocampherenane sesquiterpenoids from Illicium tsangii. [CrossRef] [PubMed]

190. Ngo, K.S.; Wong, W.T.; Brown, G.D. Muurolane sesquiterpenes from Illicium tsangii. [CrossRef] [PubMed]

191. Ngo, K.S.; Brown, G.D. Allohimachalane, seco-allohimachalane and himachalane sesquiterpenes. [CrossRef] [PubMed]

192. Ngo, K.S.; Brown, G.D. Asplenioides and Porella canariensis. J. Hattori Bot. Lab. 2005, 94, 197–204.

193. Nagashima, F.; Matsumura, N.; Ashigaki, Y.; Asakawa, Y. Chemical constituents of the liverworts Bryopteris filicina, Plagiochila asarifolia and porella canariensis. J. Hattori Bot. Lab. 2003, 94, 197–204.

194. Kung, A.; Saha, S.; Akuwalia, V.; Walia, S. Plant growth inhibitory terpenes from Eupatorium adenophorum. J. Appl. Bot. Food Qual. 2013, 86, 33–36.

195. Wang, C.F.; Zhao, Y.; Liu, Y.Z.; Zhang, Z.Z. Occurrence and biological activities of eremophilane-type sesquiterpenes. Chem. Res. Chinese Univ. 2009, 25, 480–484.

196. He, L.; Hou, J.; Fan, C.Q.; Liao, S.G.; Yue, J.M. A novel eudesmane sesquiterpenoid from Schisandra sphenanthera stems. Chem. Nat. Comp. 2011, 47, 713–717. [CrossRef]

197. Adio, A.M.; König, W.A. Sesquiterpene constituents from the essential oil of the liverwort Plagiokila asplenioides. Phytochemistry 2005, 66, 599–609. [CrossRef]

198. Nagashima, F.; Suzuki, M.; Takaoka, S.; Asakawa, Y. New acorane- and cuparane-type sesqui- and new labdane- and seco-labdane-type diterpenoids from the Japanese liverwort Jungermannia infusca (Mitt.) Steph. Tetrahedron 1999, 55, 9117–9121. [CrossRef]

199. Wang, C.F.; Zhao, Y.; Liu, Y.Z.; Zhang, Z.Z. New sesqui- and diterpenoids from the Japanese liverwort Jungermannia infusca (Mitt.) Steph. Tetrahedron 1999, 55, 9117–9121. [CrossRef]

200. circa 1990. Heterocycles 1990, 37, 622–630. [CrossRef] [PubMed]

201. He, L.; Hou, J.; Fan, C.Q.; Liao, S.G.; Yue, J.M. The first limonoid peroxide in the Meliaceae family: Walsuronoid A from Walsura robusta. Org. Lett. 2007, 9, 2353–2356. [CrossRef]

202. Chen, G.F.; Li, Z.L.; Tang, C.M.; He, X.; Chen, K.; Pan, D.J.; Hu, C.Q.; McPhail, D.R.; McPhail, A.T.; Lee, K.H. Structure and stereochemistry of pseudolarolide-I, a novel cytotoxic peroxytriterpene dilactone from Pseudolarix kaempferi. Heterocycles 1990, 31, 1903–1906.

203. Zhou, T.; Zhang, H.; Zhu, N.; Chiu, P. New triterpenoid peroxides from Pseudolarix kaempferi. Tetrahedron 2004, 60, 4931–4936. [CrossRef]

204. Ali, Z.; Khan, L.A.; Frondcek, F.R. Revision of the structure of podocarpaside E from Actaea podocarpa. Acta Crystallograph. 2007, 63, e2101–e2103.

205. Ding, Y.; Li, C.; Kim, J.H.; Lee, Y.M.; Hyun, J.H.; Kang, H.K.; Kim, J.A.; Min, B.S.; Kim, Y.H. Triterpenoid compounds isolated from Acer mandshuricum and their anti-inflammatory activity. Bioorg. Med. Chem. Lett. 2010, 20, 1528–1531. [CrossRef] [PubMed]

206. Ma, Y.P.; Li, N.; Gao, J.; Fu, K.L.; Qin, Y.; Li, G.Y.; Wang, J.H. A new peroxy-multiflorane triterpene ester from the processed seeds of Trichosanthes kirilowii. Helv. Chim. Acta 2011, 94, 1881–1889. [CrossRef]

207. Chiang, Y.M.; Kuo, Y.H. New peroxy triterpenes from the aerial roots of Ficus microcarpa. J. Nat. Prod. 2001, 64, 436–439. [CrossRef] [PubMed]
267. Salas, P.F.; Herrmann, C.; Orvig, C. Metalloantimalarials. *Chem. Rev.* 2013, 5, 3450–3492. [CrossRef]
268. Vizer, S.A.; Sycheva, E.S.; Quntar, A.A.A.; Kurmankulov, N.B.; Yerzhanov, K.B.; Dembitsky, V.M. Propargylic sulfides: Synthesis, properties, and application. *Chem. Rev.* 2015, 115, 1475–1502. [CrossRef]
269. Barnett, D.S.; Guy, R.K. Antimalarials in development in 2014. *Chem. Rev.* 2014, 114, 11221–11241. [CrossRef]
270. Dembitsky, V.M.; Quntar, A.A.A.; Srebnik, M. Natural and synthetic small boron-containing molecules as potential inhibitors of bacterial and fungal quorum sensing. *Chem. Rev.* 2011, 111, 209–237. [CrossRef]
271. Smoum, R.; Rubinstein, A.; Dembitsky, V.M.; Srebnik, M. Boron containing compounds as protease inhibitors. *Chem. Rev.* 2012, 112, 4156–4220. [CrossRef] [PubMed]
272. Dembitsky, V.M. Anticancer activity of natural and synthetic acetylenic lipids. *Lipids* 2006, 41, 883–924. [CrossRef] [PubMed]
273. Siddiq, A.; Dembitsky, V. Acetylenic anticancer agents. *Anti-Cancer Agents Med. Chem.* 2008, 8, 132–170. [CrossRef] [PubMed]
274. Dembitsky, V.M.; Levitsky, D.O. Acetylenic terrestrial anticancer agents. *Nat. Prod. Commun.* 2006, 1, 405–429. [CrossRef]
275. Kuklev, D.V.; Dembitsky, V.M. Epoxy acetylenic lipids: Their analogues and derivatives. *Prog. Lipid Res.* 2014, 56, 67–91. [CrossRef]
276. Levitsky, D.O.; Dembitsky, V.M. Anti-breast cancer agents derived from plants. *Nat. Prod. Bioprosp.* 2015, 5, 1–16. [CrossRef]
277. Dembitsky, V.M.; Levitsky, D.O.; Gloriozova, T.A.; Poroikov, V.V. Acetylenic aquatic anticancer agents and related compounds. *Nat. Prod. Commun.* 2006, 1, 773–811. [CrossRef]
278. Abu-Lafi, S.; Dembicki, J.W.; Goldshlag, P.; Hanuš, L.O.; Dembitsky, V.M. The use of the Cryogenic GC/MS and on-column injection for study of organosulfur compounds of the Allium sativum. *J. Food Composit. Anal.* 2004, 17, 235–245. [CrossRef]