Naturally Occurring Peroxides with Biological Activities

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Abstract: New natural peroxides that have potent biological activities with novel diverse structures are reviewed with classification as secondary metabolites such as terpenes, polyketides, phenolics, and hydroperoxides. These compounds, isolated mainly from medicinal plants and marine sponges, are valuable sources in the drug discovery for particularly antitumor and antimalarial agents.

KeyWords: Peroxide, Natural product, Terpenes, Polyketides, Phenolics, Hydroperoxides.

INTRODUCTION

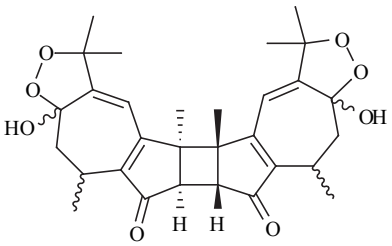
More than 50% of world marketed drugs have their origin of the nature. Natural products, of which structural diversity is so broad, are good sources for the effective discovery of medicinal agents with decreased toxicity. Over the past decades, substantial progress has been made in research on the natural products for the medicinal agents. Naturally occurring peroxides have gained much interest due to their structural diversity and pharmaceutical properties

Artemisinin and its analogues have been studied for long time because of their potency against drug-resistant forms of Malaria, especially *Plasmodium falciparum*[1]. Although not thoroughly known, the reaction mechanism of this compound [2] reveals the possibility of pharmaceutical uses toward other diseases including cancer [3] and AIDS [4] etc. Moreover, many simpler peroxides have been found to exhibit wide activities such as antimalarial, cytotoxic, and antiviral activities. Generally, acyclic peroxides, of which simplest form is hydrogen peroxide, are unstable and can be easily broken by bases and metals. But many cyclic peroxides are stable under harsh condition. For example, artemisinin is stable under boiling, or base such as sodium borohydride, while its peroxide bond is broken under special chemical environment. In biological system, the radical or ion generated by selective breakage of peroxide bond play important role, which can be the cause of the biological activities [5].

Recently, two reviews of the chemistry of cyclic peroxides have been published by Casteel [6a], McCullough and Nojima [6b]. New natural peroxides reported from 2000 until 2001 that have potent medicinal activities with novel diverse structures were reviewed in this article. These compounds, isolated mainly from medicinal plants and marine sponges, in this review have been classified as secondary metabolites such as terpenes, polyketides, phenolics, and hydroperoxides. Especially terpenes have gained much interest due to their significant biological activities along with their structural diversity.

TERPENES

From the leaves of *Xylopia vielana* (Annonaceae), the dimeric guaiane peroxide vielanin C was isolated and structurally elucidated as **1** [7]. The structure of **1** contains two peroxide bonds form probably via reactions of **2** with singlet oxygen, and symmetric cyclobutane formally generated from two equal guaiane moieties (**3**) by [2+2] cycloaddtion. The biological activities of this compound were not reported, but the bark and leaves of *X. vielana* are used in folk medicine for the treatment of rheumatism and pain. Actually, this compound **1** is interesting due to its structural symmetry and rare 3-hydroxy 1, 2-dioxane moiety.



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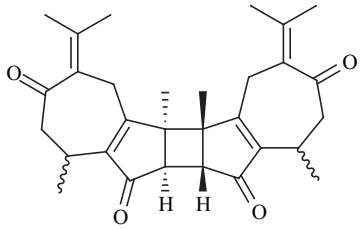

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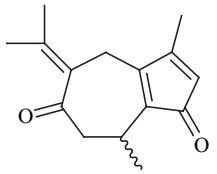

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Fig. (1). Terpene-type peroxides from the leaves of *Xylopia vielana.*

A new peroxy sesquiterpenoid **4** was isolated from the ether extract of Belgian *Scapania undulata* [8]. The absolute

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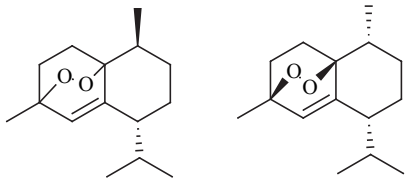
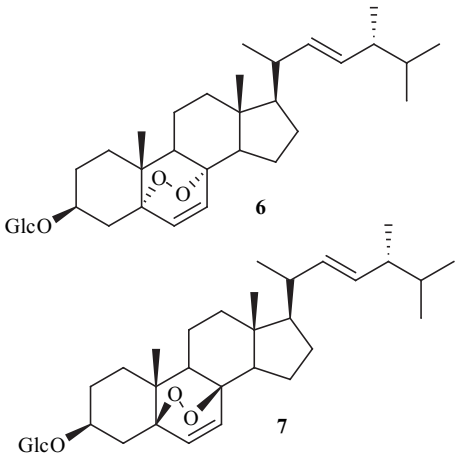
configurations at peroxide oxygen were not clearly defined. But from spectral data, this compound was proposed to be a stereoisomer of previously known peroxide **5** [9].



4 **5**

Fig. (2). Terpene-type peroxides from the ether extract of Belgian *Scapania undulata.*

Some new ergostane-type peroxides **6**, **7** were isolated [10] from the ethanol extract of *Lactarius volemus* (Russullaceae) which inhibits the growth of several tumor cell lines *in vitro* [11].



6 **7**

Fig. (3). Ergostane-type peroxides from the ethanol extract of *Lactarius volemus.*

From *Achillea setacea*, the peroxide **8** with unusual structure was isolated in addition of known sesquiterpenes [12].

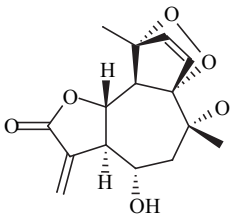


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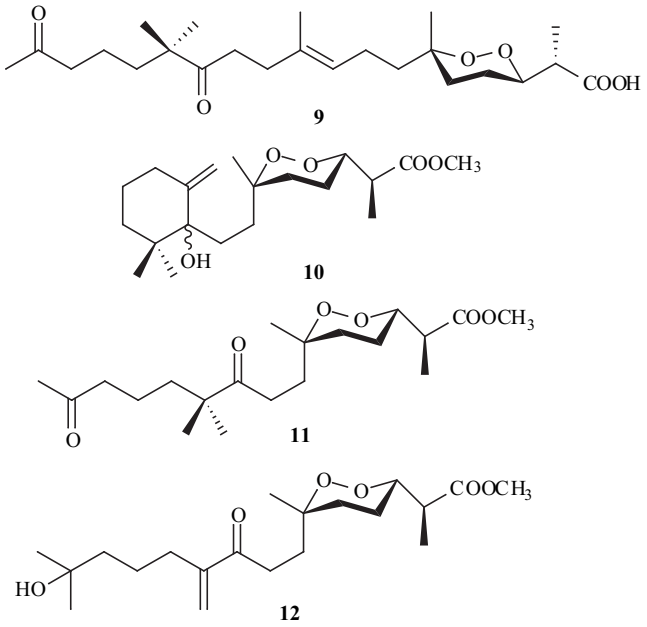
Fig. (4). Terpene-type peroxides from *Achillea setacea.*

Besides the plants, marine sponges are known to produce terpene peroxides and related metabolites that are potential lead compounds for the development of new drugs. They display a wide range of bioactivity including antimicrobial[13], antiviral[14], cytotoxicity[14], and antimalarial activities[15, 16]. One new norsesterterpene cyclic peroxide, aikupikoxide A (**9**) and three new norditerpene cyclic peroxides, aikupikoxide B-D (**10**-**12**) were isolated from the lipophilic extract of the Red Sea sponge *Diacarnus erythraenus* [17]. These four compounds showed activity of IC_{50} > 1μg/mL against the three types of cancer cells including murine leukemia (P-388: ATCC: CCL 46), human lung carcinoma (A-549: ATCC: CCL 8), and human colon carcinoma (HT-29: ATCC: HTB 38).

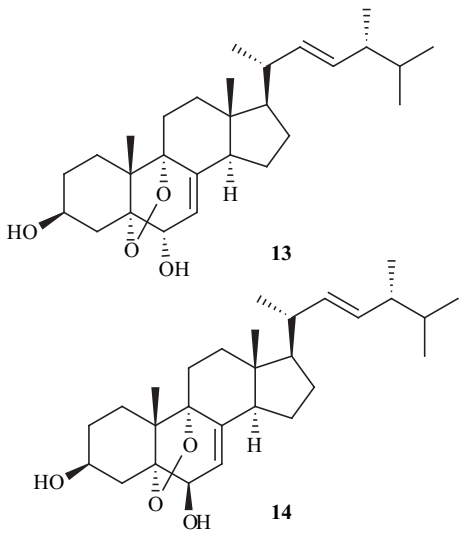


9 **10** **11** **12**

Fig. (5). Aikupikoxide-type peroxides from the lipophilic extract of the Red Sea sponge Diacarnus erythraenus.

Aikupikoxide A (**9**), also named muqubilone by Hamann, possesses *in vitro* antiviral activity against HSV-1 as shown by protecting a confluent nonproliferating monolayer of Vero African green monkey kidney cells from the cytopathic effect of the virus with ED_{50} of 7.5 μg/mL. But it did not show *in vitro* antimalarial activity toward drug-resistant *Plasmodium falciparum* [18].

Two new sterols **13** and **14** were isolated from edible mushroom *Panellus serotinus*. Compound **13** was also isolated from other edible mushroom *Lipista nuda* [19].



13 **14**

Fig. (6). Sterol-type peroxides from edible mushroom *Panellus serotinus.*

POLYKETIDES

Antiproliferative bioassay-guided fractionation of the organic extract of a previously undescribed species of ascidian from the genus *Stonlonica* yielded two new fatty acid-derived cyclic peroxides, stolonic acids A(**15**) and B(**16**) [20]. Both compounds exhibited antiproliferative activity against selected human melanoma (LOX) and ovarian (OVCAR-3) tumor cell lines, with IC_{50} values of approximately 0.05-0.1 μg/mL.

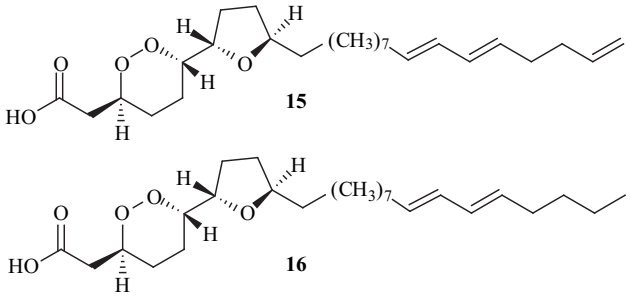


Fig. (7). Polyketide-derived peroxides from the organic extract of a previously undescribed species of ascidian from the genus *Stonlonica.*

Two new cyclic peroxides, plakortolide F (**17**) and G (**18**) were isolated from the sponge *Plakinastrella onkodes* collected at Jamaica [21]. Plakortolide F (**17**) displayed no *in vitro* activity while plakortolide G (**18**) exhibited potent inhibitory activity against *Toxoplasma gondii* in HFF cells at 10 μM concentration and represents the first marine natural product reported with *T. gondii* inhibitory activity. It is well-known that Plakinidae have yielded peroxylactones, as well as numerous other peroxide containing metabolites and the plakortolides are cytotoxic to tumor cells [22].

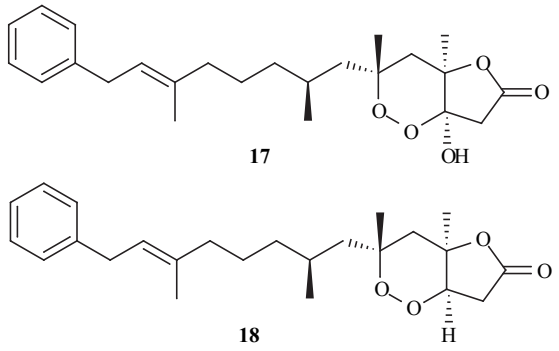


Fig. (8). Plakortolides from the sponge *Plakinastrella onkodes.*

Two new acetogenin peroxides, named peroxyacarnoic acids C (**19**) and D (**20**) and one previously known [23] metabolite peroxyacarnoic acid A (**21**) were isolated from the sponge *Acarnus bicladotylota*, Hoshino [24].

Two new five-membered-ring peroxide acids, plakinic acid F (**22**), epiplakinic acid F (**23**) and one new peroxide-lactone, plakortolide F (**24**) were isolated from a sponge of the genus *Plakinastrella* collected from Felicite Island [25]. The free acids **22** and **23** exhibit moderate antifungal activity against *Candida albicans* with minimum inhibitory

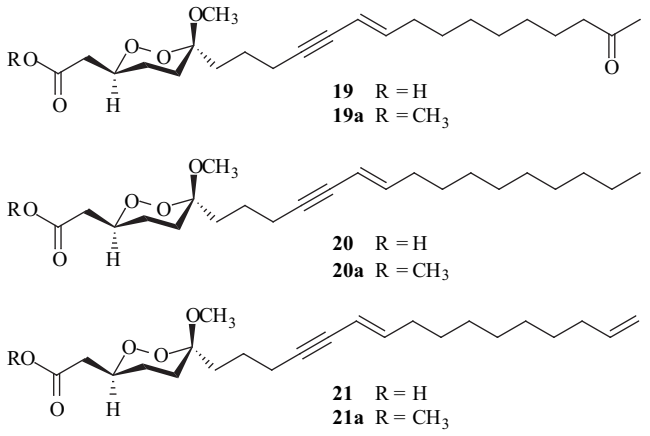


Fig. (9). Peroxyacarnoic acids from the sponge *Acarnus bicladotylota.*

concentrations of 25μg/mL (SDB: using sabouraud dextrose broth as growing media) [26] and 3.1μg/mL (RPMI: using buffered RPMI as growing media) [27] for **22**, and 25μg/mL (SDB) and 6.25μg/mL (RPMI) for **23**, respectively. Both also showed moderate *in vitro* inhibition of *Aspergillus fumigatus* with IC_{90}'s of 25μg/mL.

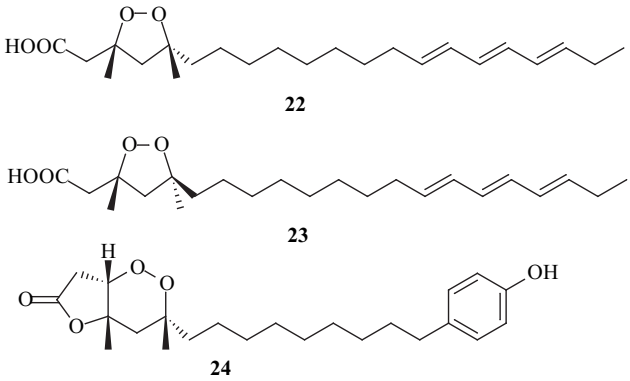


Fig. (10). Plakortolides from a sponge of the genus *Plakinastrella.*

The cytotoxic cyclic peroxides, methyl capucinoate A (**25**) and **26** were isolated from the Dominican marine sponges *Plakinastrella onkodes* by cytotoxicity-guided fractionation [28].

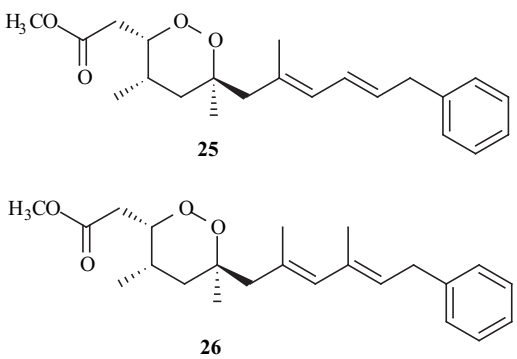
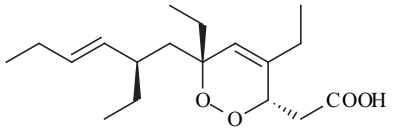


Fig. (11). Capucinoates from the Dominican marine sponges *Plakinastrella onkodes.*

Other simpler types of peroxides were isolated from the Okinawan sponge *Plakortis lita* via activity-guided fractionation [29]. Haterumadioxin A (**27**) and B (**28**) were evaluated against a human cancer cell line panel to show significant cytotoxicity against P833 cells, with IC_{50} values of 11 and 5.5ng/mL, respectively. The stereochemistry of haterumadioxin B was not cleared defined, but it is a stereoisomer of haterumadioxin A.



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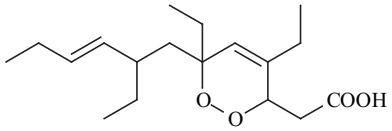

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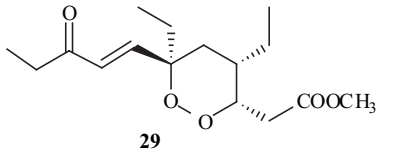
Fig. (12). Haterumadioxins from the Okinawan sponge *Plakortis lita.*

From an undescribed sponge of the genus *Plakortis* collected at Jamaica, four new cyclic peroxides, plakortolide I (**29**), J (**30**), K (**31**), and L (**32**) were isolated [30]. Plakortolide I is the first report of a polyketide-derived peroxide with an α,β-unsaturated ketone moiety in the side chain and exhibits significant antimalarial activity against the W2 clone of *Plasmodium falciparum* with an IC_{50} value of 0.57μg/mL.



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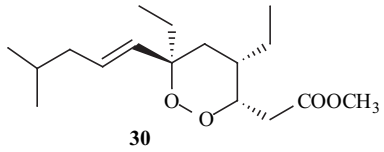

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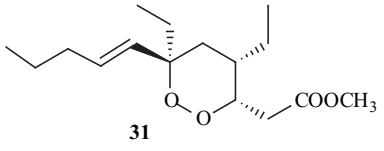

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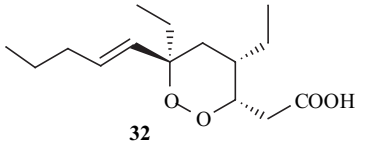

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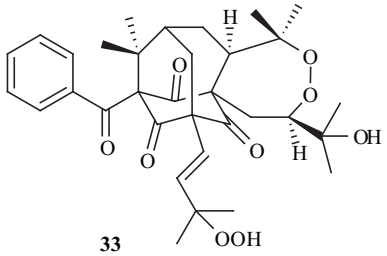
Fig. (13). Plakortolides from an undescribed sponge of the genus *Plakortis.*

PHENOLICS

As the rare examples of phenolic-derived peroxides, two new prenylated benzophenone derivatives that have peroxide bond were isolated from the extracts of the fruit of *Clusia havetiodes* var. *stenocarpa*. 33-Hydroperoxyisoplukenetione C **(33)** and previously-known plukenetione C (**34**) [31] have 7-membered peroxide ring.



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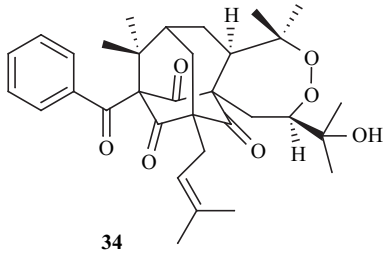

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Fig. (14). Plukenetiones from the extracts of the fruit of *Clusia havetiodes* var. *stenocarpa.*

15,16-Dihydro-16-hydroperoxyplukenetione F (**35**) containing only acyclic peroxide bond was also isolated from the extracts of the fruit of *Clusia havetiodes* var. *stenocarpa* with **33** and **34** [32].

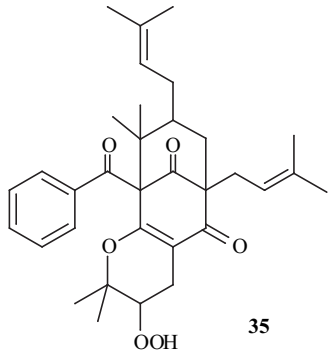

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Fig. (15). The structure of 15,16-dihydro-16-hydroperoxy-plukenetione F.

HYDROPEROXIDES

Though more unstable than endoperoxides, compounds having hydroperoxy group also have been isolated from various natural resources with significant biological activities.

Diterpenes with the dolabellane skeleton were originally isolated from the herbivorous sea hare *Dolabella californica*

[33] and subsequently from the brown algae *Glossophora galapagensis* [34], upon which the sea hare feeds, *Dictyota dichotoma, D. pardarlis*, and *Dilophus fasciola*. In the search for bioactive substances from marine organisms, the Formosan soft coral *Clavularia inflata* Schenk (Stolonifera) was studied because CH_2Cl_2 extracts showed significant cytotoxicity to various cell lines. Bioassay-guided fractionation resulted in the isolation of six new cytotoxic dolabellane diterpenes including one peroxide, (1R*,7R*)-7-hydroperoxydolabella-4(16),8(17),11(12)-triene-3,13-dione(**36**) [35].

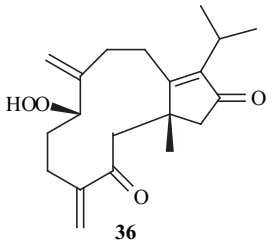

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Fig. (16). Cytotoxic dolabellane-type diterpene containing hydroperoxy group.

The highest cytotoxicity of this peroxide among the extracted 6 terpene compounds shows the importance of hydroperoxy group to the activity.

(6S)-hydroxy-(24ξ)-hydroperoxy-29-nor-3,4-seco-cycloart-4(30),25-dien-3-oic acid methyl ester(**37**), extracted from the aerial parts of *Antirhea acutata* (DC.) Urb. (Rubiaceae) [36] showed moderate inhibitory activities in cyclooxygenase-1 and -2 assays (IC_{50} 45.7 and 18.4 μM, respectively). As the former case, other four isolates from *A. acutata* with same carbon skeleton showed no inhibitory activities to cyclooxygenase.

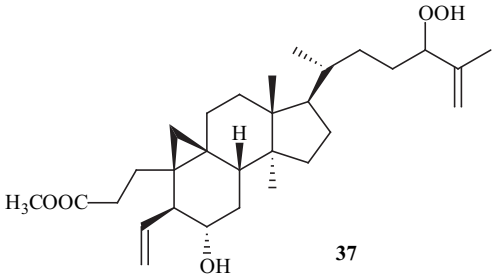

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Fig. (17). Hydroperoxycycloartdienoate from *Antirhea acutata.*

Investigation on the saponins of the flower-buds of *Panax ginseng* resulted in the isolation and structural elucidation of a pair of new 24-epimers of dammarane type saponins named ginsenoside **38** [37]. The location of hydroperoxy group of this compounds are identical with the former COX inhibitor. Further biological study on these compounds is expected.

Five new triterpenes containing peroxy group, 3β-acetoxy-12β,13β-epoxy-11α-hydroperoxyursane(**39**), 3β-acetoxy-11α-hydroperoxy-13α*H*-ursan-12-one(**40**), 3β-acetoxy-1β,11α-epidioxy-12-ursene(**41**), (20S)-3β-acetoxy-20-hydroperoxy-30-norlu-pane(**42**), and 3β-acetoxy-18α-

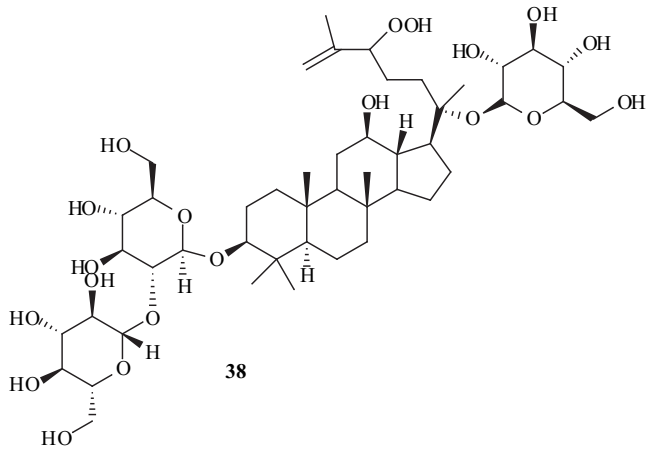

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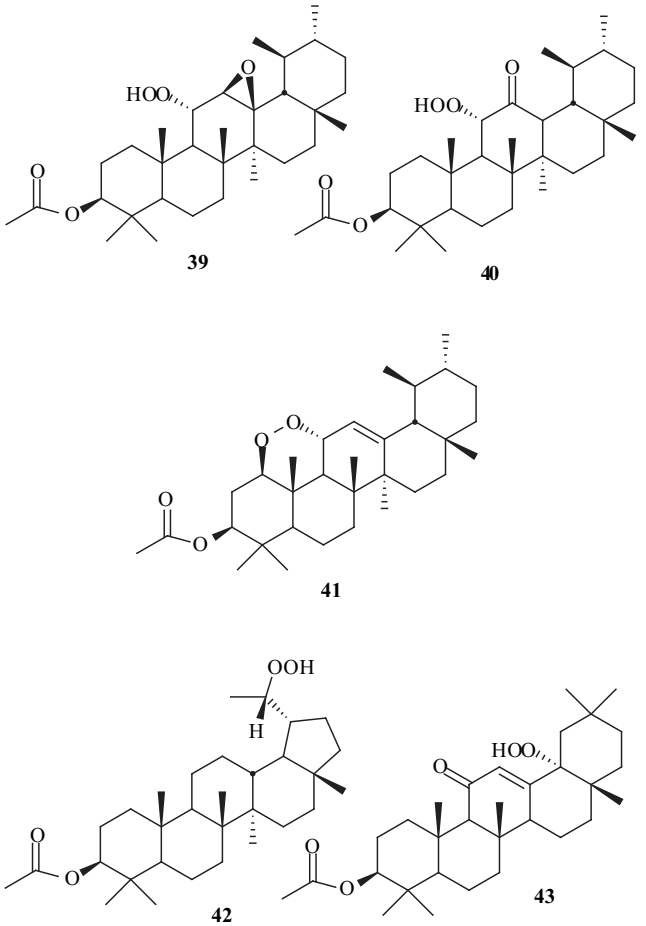
Fig. (18). Saponin-type hydroperoxide, ginsenoside I and II.

hydroperoxy-12-oleanen-11-one(**43**) were isolated [38] from the aerial roots of *Ficus microcarpa*, which is a popular ornamental plant in Taiwan [39].



39 **40**

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42 **43**

Fig. (19). Triterpenes containing hydroperoxy group from *Ficus microcarpa.*

A new carbazole alkaloid(**44**), designated as glycoborine, was isolated from the roots of *Glycosmis arborea* [40]. Its structure was elucidated as 5-methoxy-3-methylcarbazole on the basis of spectroscopic analysis and confirmed by its synthesis. But the stereochemistry is ambiguous.

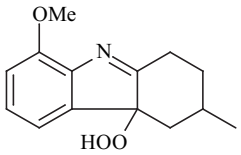

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Fig. (20). A carbazole alkaloid peroxide from *Glycosmis arborea.*

CONCLUSION

Natural peroxides, many of which exhibit antimalarial, antifungal, or antitumor activity, are reviewed in this article to show the elevated concern to this field. Peroxide bond in these compounds may be the essential to the biological activities. Characteristic structures of these compounds include terpenes, polyketides, non-cyclic hydroperoxides and even phenolics, among which the possibility of finding new drug candidate is high in the aspect of structural diversity and wide biological activity. Synthetic efforts may allow structural modification and the preparation of new derivatives to enhance the bioactivity and to reduce side effect, so that improve the understanding of structure-activity relationships. In case of artemisinin possessing endoperoxide and its derivatives, several structure-activity relationship studies [41, 42] have shown that the peroxide bonds of these compounds play the essential role to show the antimalarial activities. Steric and electostatic fields around the peroxide bond are important for the forecast of bioactivity [43]. Especially the action mechanism of these compounds [2] is different from those of other antimalarial compounds such as quinine, chloroquine, and mefloquine. From this fact, we can predict the action mechanism of anticancer activity to be same as that of antimalarial activity [3].

Among compounds cited in this review, 6-membered cyclic peroxides, especially aikupikoxides **9 – 12**, stolonic acids, **15**, **16**, and haterumadioxins, **27**, **28** show relatively high anticancer activities. Plakortolide I (**29**) exhibits significant antimalarial activity against the W2 clone of *Plasmodium falciparum*. Therefore, natural peroxides are valuable sources in the drug discovery for particularly antitumor and antimalarial agents.

ACKNOWLEDGEMENT

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