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Chemical and Biological Diversity in *Nephthea* Soft Corals in the Current Decade: A Review

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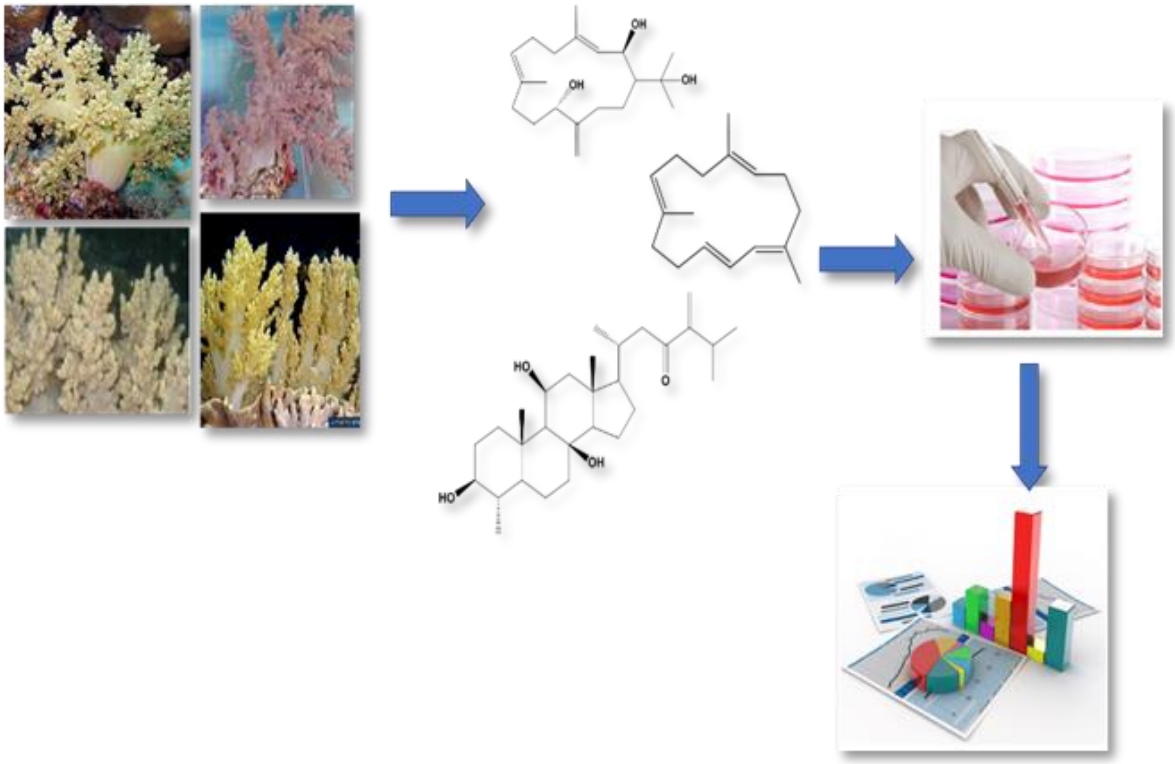
Abstract

Marine natural products play an important role within the innovation of promising compounds for drug development. The soft coral genus *Nephthea* considered a prolific source to discover potential drug candidates with biological potentials. This review provides a survey of all metabolites isolated from the genus *Nephthea* in the current decade, along with chemical structures and biological activities. The current review aimed to compare chemical and biological diversity in genus *Nephthea* soft corals. We listed 54 compounds including steroids and diterpenes. The steroids are the most abundant compounds of the genus *Nephthea* (74 %) followed by diterpenes (20%) and miscellaneous compounds (6%). The isolated compounds from genus *Nephthea* in the current decade have shown different biological activities as cytotoxic against different cancer cell lines (29 compounds), anti-inflammatory (13 compounds), antifouling (3 compounds) and antibacterial (2 compounds).

Key words
Soft corals, *Nephthea*, Diterpenes, Steroids, Cytotoxicity.



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1. Introduction

The marine soft corals are bottom-living simple animals, which exist in colonies and thrive in water with less intense light [1]. Depending on the defensive mechanisms of accumulated secondary metabolites in their bodies or secreted to the surrounding, they can survive even in hostile environments [2-4]. These invertebrates are widely distributed worldwide and found on variety of habitat, more in tropical than temperate reef, and resemble an important part of coral reefs ecosystem [5-8]. Soft corals represent a huge source of metabolites and those belong to genus *Nephthea* (Kingdom: Animalia, Phylum: Cnidaria, Class: Anthozoa, Subclass: Octocorallia, Order: Alcyonacea, Family: Nephtheidae) are evidently observed as an interesting treasure of ubiquitous constituents [9]. Members of genus *Nephthea* are arborescent colonies with branched polyparium, stiff, Polyps arranged on the terminal branches only, with supporting bundle. Sclerites are spindles and unilateral spinose spindles; surface layer of base of stalk also with capstans and derivations of capstans, colour of the colonies include whitish, brownish red, pink, yellow and purple, Zooxanthellae are present [10]. The genus *Nephthea* includes twelve species namely; *N. albida, N. armata, N. bayeri, N. brassica, N. chabrolii, N. columnaris, N. hainansis, N. erecta, N. mollis, N. Pacifica N. sinulata and N. specie*. Steroids and diterpenes were the prevailing constituents [11-13]. During a previous genus survey, Amir *et al., 2012* reported the isolation of 148 compounds [14]. Therefore, the current review updates and enriches the library of metabolites isolated from the genus *Nephthea* with all compounds isolated during the current decade, along with their biological potentials. We have reported 54 compounds including chemical structures and biological activities based on the data abstracted from the current literatures.

2. Classes of Secondary Metabolites

2.1. Steroids

Steroids are widely distributed within most species of the genus. Due to the symbiotic relationship with intracellular algae, reporting wide array of steroids with unique substitution patterns and functionalities from species of the genus *Nephthea* [15]. The literature survey demonstrated the isolation of forty steroids within the current decade.

Columnaristerols A-C (**1**-**3**) were isolated from the methylene chloride/methanol extract of *N. columnaris* which was collected from Taiwan. Columnaristerol A exhibited moderate *in-vitro* cytotoxicity against human lymphoma cell lines; MOLT-4 and SUP-T1with IC_{50} values of 18.4 and 25.3 μM, respectively [16]. Columnaristerol B and C exhibited weak anti-inflammatory activities in a human neutrophil model with IC_{50} values higher than 10 μM [17]. Chemical analysis of the methylene chloride extract of *N. mollis* collected from Hurghada, Egypt, led to identification of ten 4*α*-methylated steroidal compounds; 23-acetoxy-4*α*, 24-dimethyl-5*α*-cholest-24(28)-en-3*β*, 8*β*, 11*β*-triol (**4**), (22E,24R)-4*α*,23,24-trimethyl-5*α* -cholest-22-en-3*β*,8*β*,11*β* –triol (**5**), (22Z)-4*α*,24-dimethyl-5*α* -cholest-22-en-3*β*,8*β*,11*β* –triol (**6**), 4*α*,24-dimethyl-5*α* -cholest-24(28)-en-3*β*,8*β*,18-triol (**7**), (22E,24R)-4*α*,24-dimethyl-5*α*-cholest-22-en-3*β*,8*β*,18-triol (**8**), (22E)- 4*α*,24-dimethyl-5*α* -cholesta-22,24(28)-dien-3*β*,8*β*,18-triol (**9**), (22E,24R)-4*α*,24-dimethyl-5*α*-cholest-22-en-3*β*,8*β*,11*β* –triol (**10**), nebrosteroid A (**11**), nebrosteroid D (**14**) and nebrosteroid M (**22**). Moreover, compound (**4**), (**5**) and (**7**) showed significant cytotoxicity against K-562 human chronic myelogenous leukemia cell line with IC_{50} of 5.4 ± 1.1 μM, 7.8 ± 0.7 μM and 8.6 ± 0.7 μM, respectively. In addition, these compounds displayed moderate toxicity against the human lung cancer cell line A-549 with IC_{50} values higher than 10 μM [18]. From the acetone fraction of *N. chabrolii* collected from Taiwan, Huang *et al.*, isolated nebrosteroids A-E (**11**-**15**) and nebrosteroids G-H (**16**-**17**), all of which showed anti-inflammatory activity. Compounds (**11**-**13**) at a concentration of 10 μM, reduced iNOS levels by 10.7 ± 0.5, 9.5 ± 1.0, 0 ± 0 and 32.9 ± 6.7 respectively. Compounds (**14**), (**15**) and (**17**) reduced iNOS levels to 0, 43.2 ± 7.8 and 76.8 ± 9.5 respectively and reduce COX-2 to 63.8 ± 10.8, 57.3 ± 5.2 and 72.1 ± 10.6, respectively [3]. Cheng *et al*, isolated four sterols; nebrosteroid I-L (**18**-**21**) from the acetone fraction of the *N. chabrolii* that collected from Taiwan. Moreover, compounds (**18**-**21**) displayed remarkable anti-inflammatory activity against RAW 264.7 macrophages [12]. The nebrosteroids N–S (**23**-**28**) were isolated from the acetone extract of *N. chabrolii*, also collected from Taiwan, the isolated compounds showed potent cytotoxic activities against mouse lymphocytic leukemia P-388 cell line with ED_{50} of 1.0, 1.1 and 1.2 μg/mL, respectively. Unfortunately, they were ineffective against human cytomegalovirus (HCMV) using human embryonic lung (HEL) cell line [19, 20]. Moreover, from the ethyl acetate fraction of the soft coral *N. erecta* that collected also from Taiwan; nephtheasteroid A (**29**) and nephtheasteroid B (**30**) were isolated. These compounds exhibited weak *in-vitro* cytotoxic activities against human chronic myelogenous leukemia (K-562), human acute lymphocytic leukemia (Molt-4), human T lymphoblastoid (Sup-T1) and human leukemic monocyte lymphoma (U937), with IC_{50} values more than 20 μM, using the MTT assay [21]. Furthermore, 4*α*, 24-dimethyl-5*α*, cholest-8*β*, 18-dihydroxy, 22E-en-3*β*-ol (**31**) was isolated from the methylene chloride extract of *Nephthea species*, collected from Hurghada, Egypt, and it showed weak cytotoxicity against MCF-7, the breast cancer cell line [22]. Nephthoacetal (**32**) with its two derivatives; (18*S*)-18-*O*-acetylnephthoacetal (**33**) and (18*R*)-18-*O*-acetylnephthoacetal (**34**) were isolated from the alcoholic extract of *Nephthea sp.*, collected from China. Compound (**32**) showed significant anti-fouling activity against the larvae of *Bugula neritina* L. with EC_{50} value of 2.5 μg/mL, while compounds (**33**) and (**34**) showed no anti-fouling potentials. On the opposite hand, compound (**33**) showed *in-vitro* cytotoxicity against the human cervical neoplastic cell line (HeLa), followed by compounds (**32**) and (**34**), with IC_{50} values of 10.2, 12.4 and 19.5 μg/mL, respectively [23]. Zhang et al, have isolated (12*β*, 22*R*)-12-acetoxy-22-hydroxy-cholesta-1,4-dien-3-one (**35**) and its derivatives; (12*β*, 22*R*)-12, 22-diacetoxy-cholesta-1, 4-dien-3-one (**36**), (*22R*)-18, 22-diacetoxy-cholesta-1, 4-dien-3-one (**37**), (12*β*, 22*R*)-12-hydroxy-22-acetoxy-cholesta-1, 4-dien-3-one (**38**) and (20*R*, 22*R*)-20-hydroxy-22-acetoxy-cholesta-1, 4-dien-3-one (**39**) from the alcoholic extract of *Nephthea sp.*, collected from China. The isolated compounds showed cytotoxicity against HeLa cells with IC_{50} values 7.52 ± 0.21 to 18.73 ± 0.77 μg/mL [24]. Tabot *et al.*, isolated compound; pregna-1, 4, 20-trien-3-one (**40**) from the DCM fraction of *Nephthea sp.* It showed inhibitory activity against human colon adenocarcinoma SW-480 cells (IC_{50} = 2.4 μg/ml) [25]. Here, we compile the steroids isolated from the genus *Nephthea* in the current decade as shown in table {**1}** and figures {**1- 3**}.

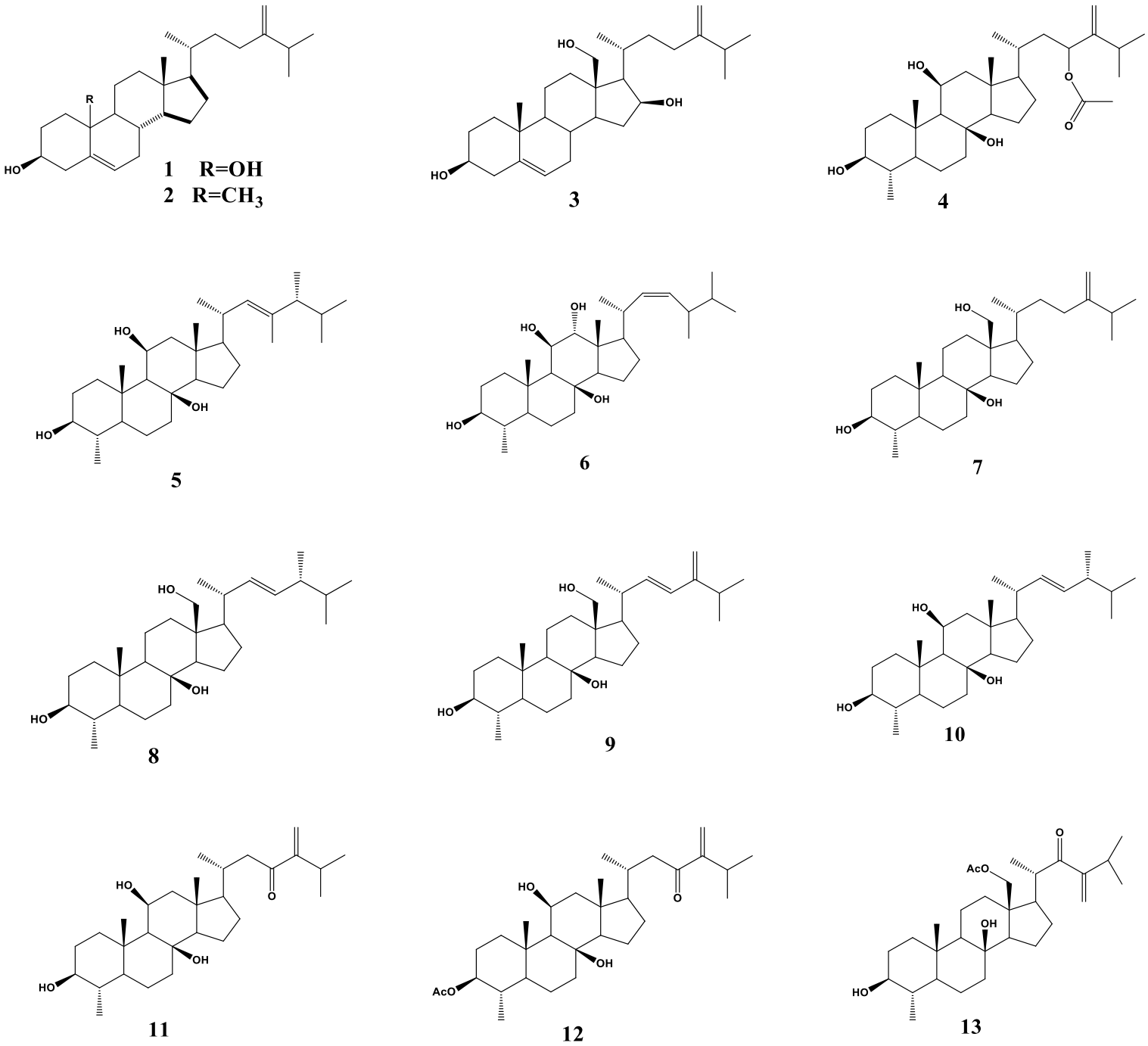

Figure 1. Chemical structures of compounds (**1-13**)

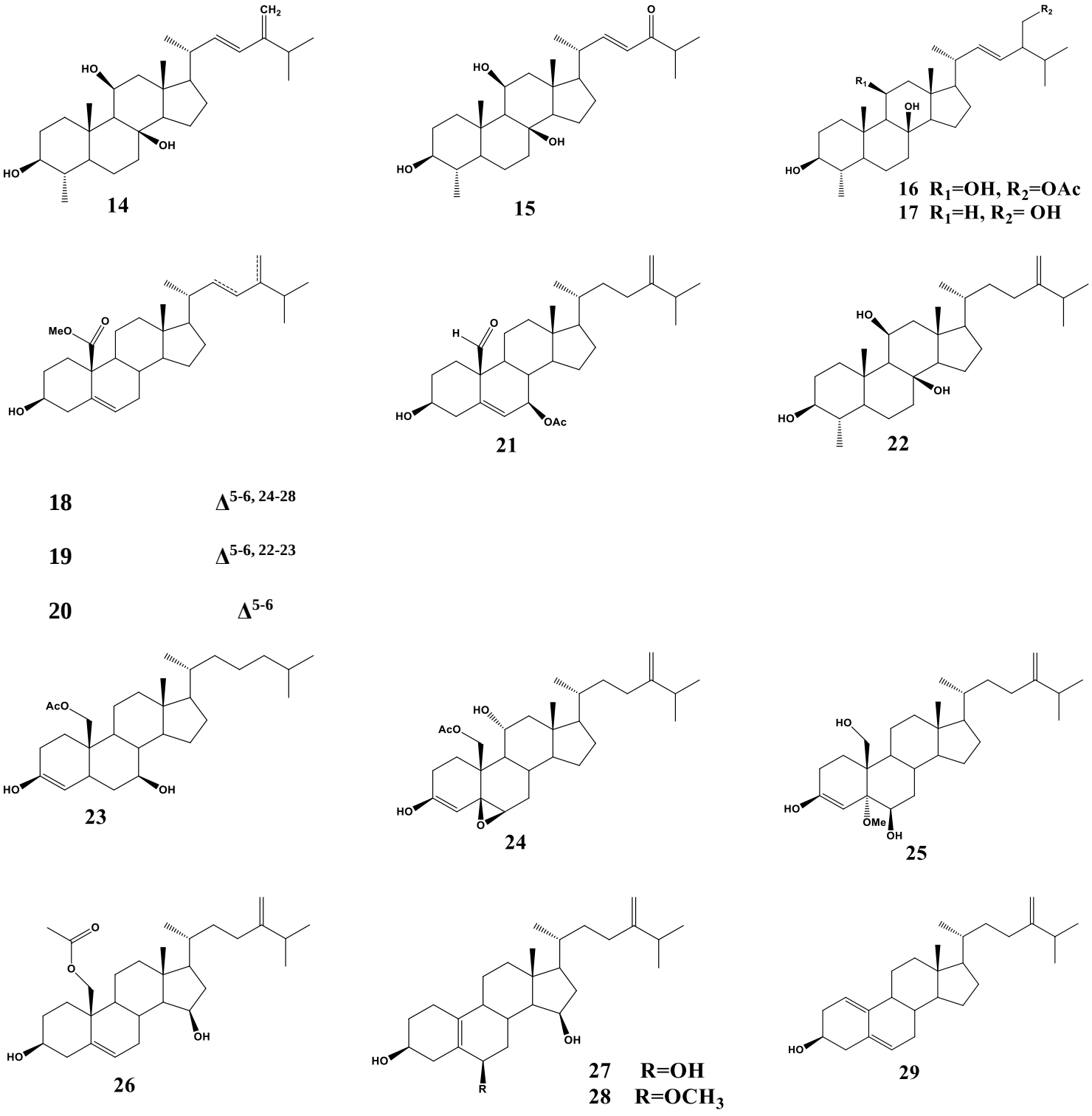

Figure 2. Chemical structures of compounds (**14-29**)

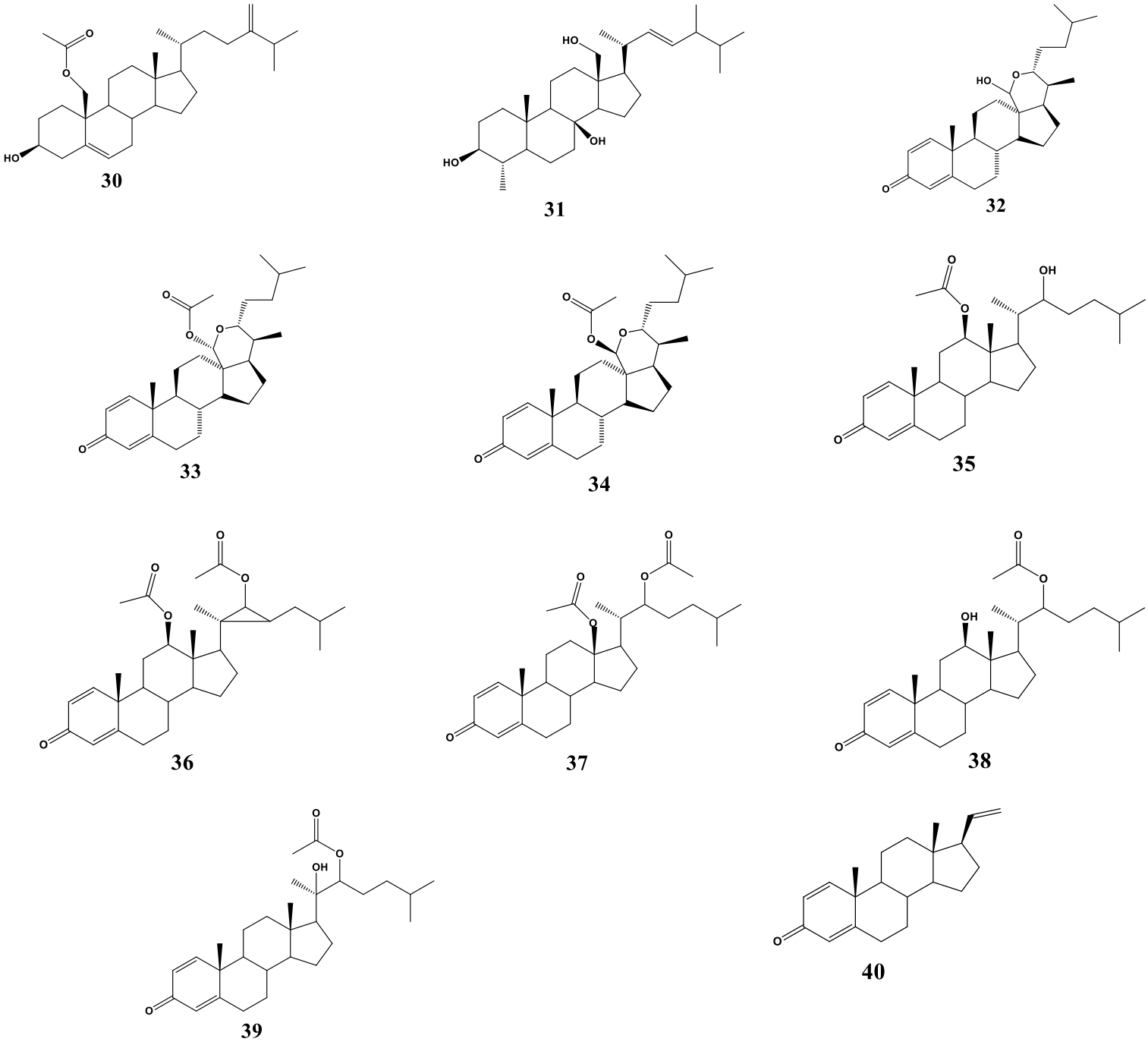

Figure 3. Chemical structures of compounds (**30-40**)

2.2. Diterpenes

The diterpenes are biologically active marine substances occurring mainly in sponges, algae, coelenterates, and mollusks. Marine diterpenes demonstrated clear structural distinctions from terraneous diterpenes. They are characterized by higher mass and uncommon functional groups[15]. Eleven bioactive diterpenes were isolated from soft corals of the genus *Nephthea* in the current decade figure {**4**}. Three cembrane diterpenes; namely 6-acetoxy-7, 8-epoxy-10-hydroxy-nephthenol acetate (**41**), 7, 8-epoxy-10-hydroxy-nephthenol acetate (**42**) and 10-hydroxy-nephthenol acetate (**43**) were isolated from the alcoholic extract of *N. sp*ecies, collected from Malaysia. Compound (**41**) showed remarkable antibacterial activity against *S. aureus* and *E. coli* with a MBC/MIC ratio of 2.6 and 3.2, respectively, revealing a bactericidal antibiosis. Similarly, compound (**47**) showed bacteriostatic antibiosis with a ratio of 6.2 against both bacteria. Additionally, compounds (**41**) and (**47**) showed cytotoxic activities against Hela and MCF-7 cell lines, with IC_{50} values of (41.2 and 24.3) and (127.2 and 76.1) µg/mL, respectively [26]. Moreover, columnariol A (**44**) and B (**45**); 15-hydroxycembranoid diterpenes were obtained from *N. columnaris* collected from Taiwan. Both of the compounds have weak cytotoxic activities against MOLT 4, SUP-T1, U 937, DLD-1, LNC and MCF-7, with IC_{50} > 20 µg/mL [27]. Hsiao et al., isolated three cembrane diterpenes; epoxynephthenol (**46**), 2*β*-hydroxy-7*β*, 8*α* epoxynephthenol (**47**) and 2*β*-hydroxy-11*α*, 12*β*- epoxynephthenol (**48**) from the ethyl acetate extract of *N. columnaris*, collected from Taiwan. None of the compounds (**46-48**) showed cytotoxicity against MOLT-4, SUP-T1, U 937, DLD-1, LNCaP and MCF-7 with IC_{50} values exceeding 20 µg/mL[27]. Ishii et al., reported the isolation of 6-acetoxy-7,8-epoxynephthenol acetate (**49**) from the *n*-hexane fraction of the *N. species* [28]. A new norditerpene; chabrolene (**50**) was isolated from *Nephthea sp.*, collected from Malaysia. It showed high repellent activity against the maize weevil *Sitophilus zeamais* [29]. Chabrolin A (**51**) was isolated from the methylene chloride fraction of *N. chabrolii*, collected from Taiwan and displayed cytotoxicity against P-388 with ED_{50} value of 4.21 µg/mL [30].

In the current decade, diterpenes isolated from various genus *Nephthea* members, are summarized in table {**1**} and figure {**4**}.

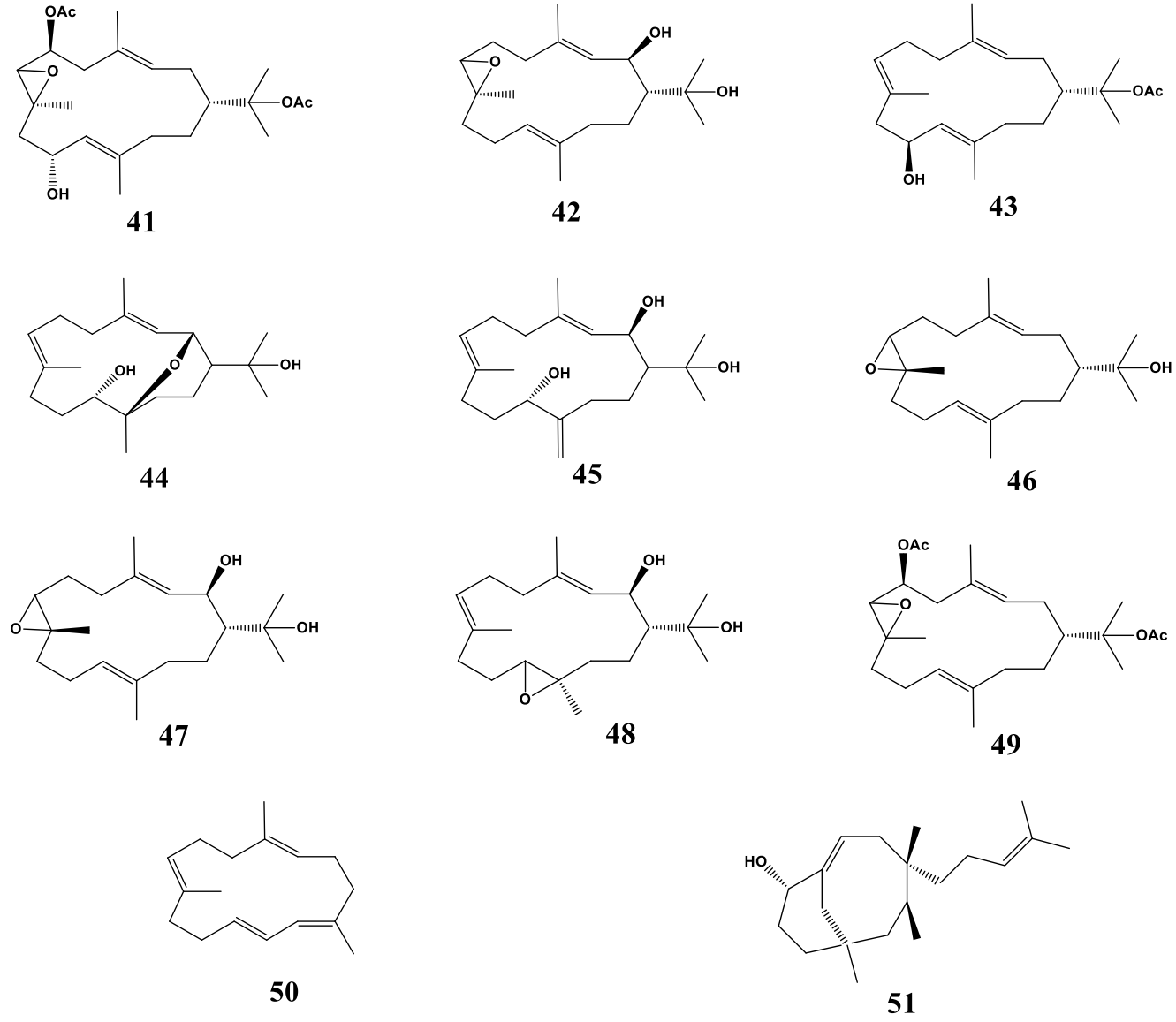

Figure 4. Chemical structures of compounds (**41-51**)

2.3. Miscellaneous compounds:

Two sesquiterpenes; Kelsoenethiol (**52**) and dikelsoenyl ether (**53**) were isolated from the methylene chloride/methanol extract of *N. erecta*, collected from Taiwan. Kelsoenethiol displayed cytotoxicity against P-388 and HT-29 cell lines with ED_{50} values of 1.4 and 1.7 μg/mL, respectively [31].

A linear tetrapeptide; Leucyl-*N*-methyl-leucyl-leucyl-*N*-methyl-leucine (**54**), was obtained from *N. sp*ecies, collected from China. It showed weak cytotoxicity against human cancer cell line A549 and human liver carcinoma Hepg2 [19]. The miscellaneous compounds isolated from various members of the genus *Nephthea* in the current decade listed in table {**1**} and figure {**5**}.

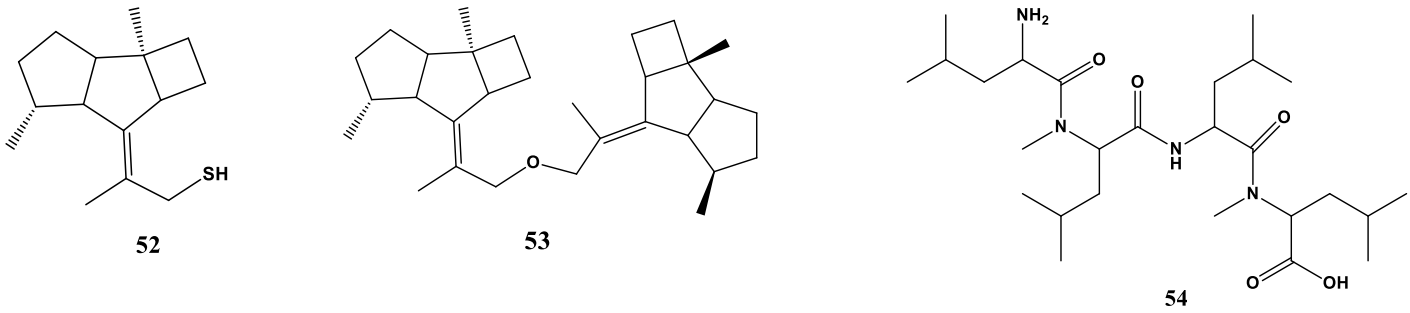

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Figure 5: Chemical structures of compounds (**52**-**54**)

Table 1: A list of different compounds isolated from the genus *Nephthea* in the current decade with its biological activities.

No Steroids	Isolated compound	Biological activities	Species	Ref.
1	Columnaristerol A	Cytotoxic activity	*N. columnaris*	[32]
2	Columnaristerol B	Anti-inflammatory activity	*N. columnaris*	[32]
3	Columnaristerol C	Anti-inflammatory activity	*N. columnaris*	[32]
4	23-Acetoxy-4*α*, 24-dimethyl-5*α*-cholest-24(28)-en-3*β*, 8*β*, 11*β*-triol	Cytotoxic activity	*N. mollis*	[18]
5	(22*E*,24*R*)-4*α*,23,24-trimethyl-5*α* -cholest-22-en-3*β*,8*β*,11*β* -triol	Cytotoxic activity	*N. mollis*	[18]
6	(22*Z*)-4*α*,24-dimethyl-5*α* -cholest-22-en-3*β*,8*β*,11*β* –triol		*N. mollis*	[18]
7	4*α*,24-Dimethyl-5*α* -cholest-24(28)-en-3*β*,8*β*,18-triol	Cytotoxic activity	*N. mollis*	[18]
8	(22*E*,24*R*)-4*α*,24-dimethyl-5*α*-cholest-22-en-3*β*,8*β*,18-triol		*N. mollis*	[18]
9	(22*E*)- 4*α*,24-dimethyl-5*α* -cholesta-22,24(28)-dien-3*β*,8*β*,18-triol		*N. mollis*	[18]
10	(22*E*,24*R*)-4*α*,24-dimethyl-5*α*-cholest-22-en-3*β*,8*β*,11*β* -triol		*N. mollis*	[18]
11	Nebrosteroid A	Anti-inflammatory activity	*N. chabrolii* *N. mollis*	[3, 18]
12	Nebrosteroid B	Anti-inflammatory activity	*N. chabrolii*	[3]
13	Nebrosteroid C	Anti-inflammatory activity	*N. chabrolii*	[3]
14	Nebrosteroid D	Anti-inflammatory activity	*N. chabrolii* *N. mollis*	[3, 18]
15	Nebrosteroid E	Anti-inflammatory activity	*N. chabrolii*	[3]
16	Nebrosteroid G	Anti-inflammatory activity	*N. chabrolii*	[3]
17	Nebrosteroid H	Anti-inflammatory activity	*N. chabrolii*	[3]
18	Nebrosteroid I	Anti-inflammatory activity	*N. chabrolii*	[12]
19	Nebrosteroid J	Anti-inflammatory activity	*N. chabrolii*	[12]
20	Nebrosteroid K	Anti-inflammatory activity	*N. chabrolii*	[12]
21	Nebrosteroid L	Anti-inflammatory activity	*N. chabrolii*	[12]
22	Nebrosteroid M		*N. mollis*	[18]
23	Nebrosteroid N	Cytotoxic activity	*N. chabrolii*	[19]

No	Isolated compound	Biological activities	Species	Ref.
24	Nebrosteroid O	Cytotoxic activity	*N. chabrolii*	[19]
25	Nebrosteroid P	Cytotoxic activity	*N. chabrolii*	[19]
26	Nebrosteroid Q	Cytotoxic activity	*N. chabrolii*	[20]
27	Nebrosteroid R	Cytotoxic activity	*N. chabrolii*	[20]
28	Nebrosteroid S	Cytotoxic activity	*N. chabrolii*	[20]
29	Nephtheasteroid A	Cytotoxic activity	*N. erecta*	[21]
30	Nephtheasteroid B	Cytotoxic activity	*N. erecta*	[21]
31	4*α*, 24-dimethyl-5*α*- cholest-8*β*, 18-dihydroxy, 22*E*-en-3*β*-ol	Cytotoxic activity	*N. sp*ecies	[22]
32	Nephthoacetal	Antifouling activity and cytotoxic activity	*N. sp*ecies	[23]
33	(18*S*)-18-*O*-acetylnephthoacetal	Antifouling activity and cytotoxic activity	*N. sp*ecies	[23]
34	(18*R*)-18-*O*-acetylnephthoacetal	Antifouling activity and cytotoxic activity	*N. sp*ecies	[23]
35	(12*β*, 22*R*)-12-acetoxy-22-hydroxy-cholesta-1,4-dien-3-one	Cytotoxic activity	*N. sp*ecies	[23]
36	(12*β*, 22*R*)-12, 22-diacetoxy-cholesta-1, 4-dien-3-one	Cytotoxic activity	*N. sp*ecies	[23]
37	(*22R*)-18, 22-diacetoxy-cholesta-1, 4-dien-3-one	Cytotoxic activity	*N. sp*ecies	[23]
38	(12*β*, 22*R*)-12-hydroxy-22-acetoxy-cholesta-1, 4-dien-3-one	Cytotoxic activity	*N. sp*ecies	[23]
39	(20*R*, 22*R*)-20-hydroxy-22-acetoxy-cholesta-1, 4-dien-3-one	Cytotoxic activity	*N. sp*ecies	[23]
40	Pregna-1,4,20-trien-3-one	Cytotoxic activity	*N. sp*ecies	[25]
Diterpenes				
41	6-Acetoxy-7, 8-epoxy-10-hydroxy-nephthenol acetate	Antibacterial activity and cytotoxic activity	*N. sp*ecies	[26]
42	7, 8-Epoxy-10-hydroxy-nephthenol Acetate	Cytotoxic activity	*N. sp*ecies	[26]
43	10-Hydroxy-nephthenol acetate	Cytotoxic activity	*N. sp*ecies	[26]
44	Columnariol A	Cytotoxic activity	*N. columnaris*	[27]
45	Columnariol B	Cytotoxic activity	*N. columnaris*	[27]
46	Epoxynephthenol	Cytotoxic activity	*N. columnaris*	[27]
47	2*β*-hydroxy-7*β*, 8*α* epoxynephthenol	Antibacterial activity and cytotoxic activity	*N. columnaris*	[27]
48	2*β*-hydroxy-11*α*, 12*β*-epoxynephthenol	Cytotoxic activity	*N. columnaris*	[27]
49	6-Acetoxy-7,8-epoxynephthenol acetate		*N. species*	[28]
50	Chabrolene	Repellent activity	*N. species*	[29]
51	A Chabrolin	Cytotoxic activity	*N. chabrolii*	[30]
Miscellaneous compounds:				
52	Kelsoenethiol	Cytotoxic activity	*N. erecta*	[31]
53	Dikelsoenyl ether	Cytotoxic activity	*N. erecta*	[31]
54	Leucyl-*N*-methyl-leucyl-leucyl-*N*-methyl-leucine	Cytotoxic activity	*N. sp*ecies	[19]

3. Conclusion and future perspectives:

Soft corals of the genus *Nephthea*, proven to be rich source for promising and biologically active compounds for the innovation of medicinal entities against different ailments. In this review, we reported 54 compounds in the current decade, along with their biological potentials based on the data collected from literatures, steroids were most abundant in the genus *Nephthea* with the percentage of (74 %) followed by diterpenes (20%) and miscellaneous compounds (6%) figure {**6**}. The isolated compounds showed diverse biological activities as; cytotoxic against different cancer cell lines (29 compounds), anti-inflammatory (13 compounds), antifouling (3 compounds) and antibacterial (2 compounds) as shown in figure {**7**}.

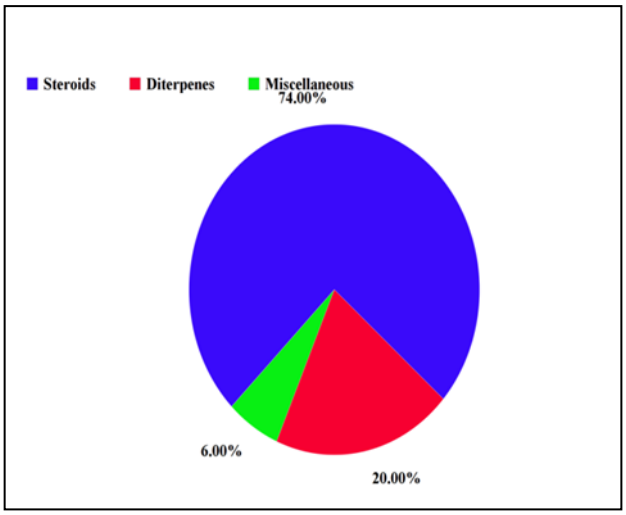

Figure 6. Percentage of different classes of metabolites distributed in the genus *Nephthea* in the current decade

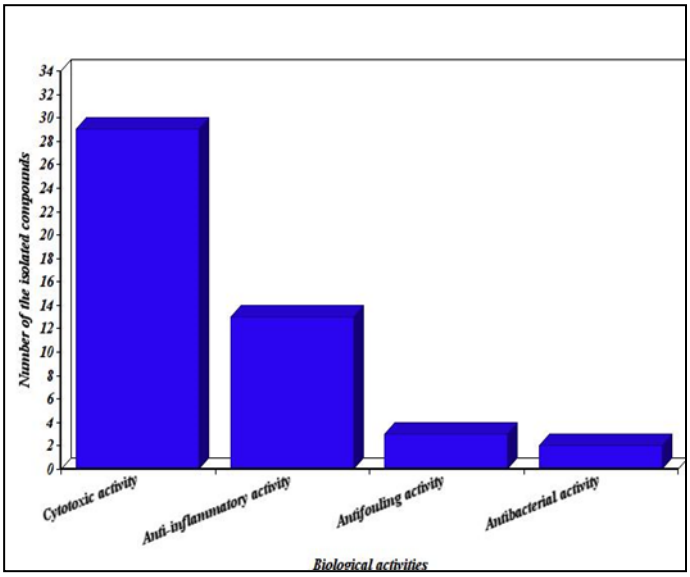

Figure 7: Biological activities of different compounds isolated from genus *Nephthea* in the current decade

It was clear that the species *N. chabrolii, N. columnaris, N. erecta, N. mollis* and *N. specie* were the most studied during the current decade, figure {**8**}. Unfortunately, other species like *N. albida, N. armata, N. bayeri, N. brassica, N. hainansis, N. pacifica* and *N. sinulata* received less attention. Accordingly, more efforts should be done in studying these species to discover more of promising compounds which may afford lead chemotherapeutic compounds that may help in treatment of different diseases.

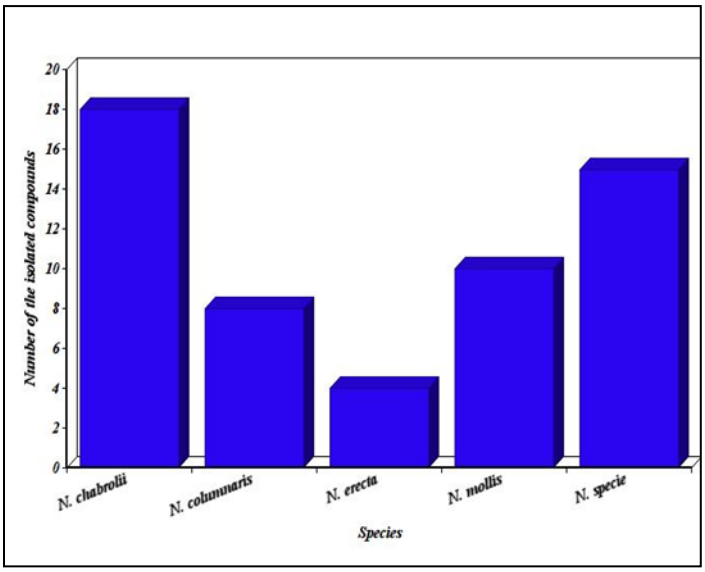

Figure 8: Number of metabolites isolated from different species of the genus *Nephthea* in the current decade

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Conflict of Interests

There is no conflict of interests regarding the publication of this paper.

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