Dactylospongia elegans—A Promising Drug Source: Metabolites, Bioactivities, Biosynthesis, Synthesis, and Structural-Activity Relationship

Sabrin R. M. Ibrahim 1,2,*, Sana A. Fadil 3, Sana A. Fadil 4, Rawan H. Hareeri 5, Sultan O. Alolayan 4, Hossam M. Abdallah 3,6 and Gamal A. Mohamed 3

Abstract: Marine environment has been identified as a huge reservoir of novel biometabolites that are beneficial for medical treatments, as well as improving human health and well-being. Sponges have been highlighted as one of the most interesting phyla as new metabolites producers. Dactylospongia elegans Thiele (Thorectidae) is a wealth pool of various classes of sesquiterpenes, including hydroquinones, quinones, and tetronic acid derivatives. These metabolites possessed a wide array of potent bioactivities such as antitumor, cytotoxicity, antibacterial, and anti-inflammatory. In the current work, the reported metabolites from D. elegans have been reviewed, including their bioactivities, biosynthesis, and synthesis, as well as the structural-activity relationship studies. Reviewing the reported studies revealed that these metabolites could contribute to new drug discovery, however, further mechanistic and in vivo studies of these metabolites are needed.

Keywords: sponges; Dactylospongia elegans; sesquiterpenes; bioactivities; biosynthesis; synthesis

1. Introduction

The marine environment is extraordinarily rich in diverse species of organisms that represent an enormous source of biometabolites, many of which have unique chemical entities not present in terrestrial sources [1–3]. The molecular diversity and exceptional complexity of marine metabolites have been highlighted in many studies [4,5]. The marine environment investigations have greatly been limited to subtropical and tropical regions, in addition, the exploration has been recently extended to colder regions. However, it is fact that many of these unique marine resources have barely been investigated.

Sponges (filter feeders, phylum Porifera) are evolutionarily ancient metazoans that occur in marine benthic, quasi-terrestrial, deep-sea, and fresh-water ecosystems [6,7]. They represent one of the important members of marine communities that have potential biotechnological and ecological roles [8,9]. They are sessile multicellular invertebrates, having an enormous amount of tiny pores on their surfaces that allow entrance and circulation of water through canals where organic particles and microorganisms are filtered out and eaten [10]. Calcarea, Demospongiae, Homoscleromorpha, and Hexactinellida are the four main classes of sponges [11]. It is noteworthy that the secondary metabolites
distribution among these four different classes of sponges is greatly varied as shown in Table 1.

Table 1. Reported secondary metabolites from the four main class of sponges [12].

| Sponge Class            | Compounds Classes                                                                 |
|-------------------------|-----------------------------------------------------------------------------------|
| Calcarea                | C$_{27}$ to C$_{29}$ $\Delta^{5,7,9(11),22}$ and C$_{27}$ to C$_{29}$ $\Delta^{5,7,22}$ sterols |
|                         | Amino alcohols                                                                    |
| Hexactinellida          | 5α(H)-Cholestan-3β-ol/cholesten-5-en-3β-ol                                       |
|                         | Ceramide glycosides                                                               |
| Homoscleromorpha        | Steroidal alkaloids                                                               |
|                         | Peroxy-polyketides                                                               |
|                         | Pyrroloquinoline, azetidine, pyrrole-2-aminoimidazole, and pentacyclic guanidine alkaloids |
|                         | Steroidal saponins and glycosides                                               |
|                         | Steroidal saponins and glycosides                                               |
|                         | Isomalabaricane triterpenoids                                                    |
|                         | Bengamide and bengazoles                                                         |
|                         | Hydroxyimino- and 3β-hydroxyethyl-A-nor-sterols                                  |
|                         | 3-Alklypyridines/3-alkylpiperidines                                              |
|                         | Renieramycins and polyacetylenes                                                 |
| Demospongiae            | Pentacyclic hydroquinones/polyrenylated benzoquinones                             |
|                         | Adenine- and cyanthiwigin diterpenes                                              |
|                         | Hypoauroxyamine (Sesquiterpene derivatives)                                       |
|                         | Diterpene thio/iso/cyanides and formamides                                       |
|                         | Sesquiterpene thio/iso/cyanides and formamides                                   |
|                         | Aaptamines and bromotyrosines                                                    |
|                         | Suberitane-derived sesterterpenes                                                |
|                         | Diterpene, sesquiterpene, and sesterterpenefurans/lactones                       |
|                         | Scalarane sesterterpenes/sesterterpene hydroquinones                             |
|                         | Thiazole polyketides                                                             |
|                         | Polybrominated diphenyl ethers                                                   |

∆: Double bond.

Sponges are devoid of any physical capacity for defense; therefore, they need to develop specific means and adaptive responses for self-protection [13]. They produce diverse secondary metabolites as defense ways against pathogenic fungi, algae, bacteria, and other predators, also to modulate and/or enable cellular communication [14]. Sponges have been known as a fertile field for the discovery of bioactive metabolites with diverse structural features that have been proven to have a beneficial potential for humans as agricultural medicines, drugs, health foods, and cosmetics [14,15].

Sponges belonging to *Dactylospongia*, particularly *D. elegans* Thiele (Thorectidae), have been vastly recognized as a wealth pool of variable metabolites with a wide array of potent bioactivities. Most of these reported metabolites are sesquiterpenes, including sesquiterpene hydroquinones, sesquiterpene quinones, and sesquiterpene tetronic acids, in addition to few sesterterpenes, sterols, and pregnanes. Further, these metabolites displayed relevant bioactivities, such as antitumor, cytotoxicity, antibacterial, and anti-inflammatory. Diverse studies focusing on the separation, characterization, and bioactivities of *D. elegans* metabolites are reported. Therefore, this works aims to summarize all reported molecules, including their activities, biosynthesis, and synthesis, as well as highlighting the structure–activity relationship studies, which could be used as an extensive reference for further studies on this sponge and its metabolites. Additionally, this work magnifies the relevance of *D. elegans* in the field of marine metabolites production and its significance in the discovery of naturally derived biometabolites. The literature search on *D. elegans* was done by collecting the information on the conducted studies, using scientific databases and websites of various journals, such as Google Scholar, ACS (American Chemical Society),
Phytochemical studies of *D. elegans* from 1992 until 2022, revealed that 101 metabolites have been separated and characterized from *D. elegans*. These metabolites are grouped according to their chemical classes into sesquiterpenes, sesterterpenes, diterpenes, sterols, pregnanes, and other metabolites which are consequently discussed (Table 2).

**Table 2.** List of reported metabolites from *Dactylospongia elegans*.

| Compound Name                  | Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country                                      | Ref.          |
|--------------------------------|------------------|----------|--------------|----------------------------------------------------|--------------|
| (-)-Ilimaquinone (1)           | CH$_2$Cl$_2$ fraction of MeOH extract | 358      | C$_{22}$H$_{30}$O$_4$ | * Similani island, Phuket, Thailand * Papua New Guinea | [16]          |
|                                | CH$_2$Cl$_2$ fraction of MeOH extract | -        | -            | Pulan Tiga, Sabah, Malaysia                         | [17]          |
|                                | CH$_2$Cl$_2$ fraction of MeOH extract | -        | -            | Pelorus Island, the Great Barrier Reef, Queensland, Australia | [18]          |
|                                | EtOAc fraction of MeOH extract       | -        | -            | Coral reef of Ishigaki Island, Okinawa, Japan      | [19]          |
|                                | CH$_2$Cl$_2$ fraction of MeOH extract | -        | -            | West Flores, Indonesia                              | [20]          |
|                                | EtOAc fraction of CH$_2$Cl$_2$ of MeOH extract | -        | -            | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia | [21]          |
|                                | 90% and 100% MeOH fraction of RP-18 CC of MeOH extract | -        | -            | Pugh Shoal, northeast of Truant Island, Australia   | [22]          |
|                                | CH$_2$Cl$_2$ fraction of H$_2$O extract | -        | -            | * Coast of Malaysia * Coast of Palau                | [23]          |
|                                | CH$_2$Cl$_2$ fraction of MeOH extract | -        | -            | West Flores, Indonesia                              | [24]          |
|                                | RP-18 CC, 60% MeOH/H$_2$O of MeOH extract | -        | -            | Towo’e Beach Tahuna Bay, Sangihe Islands North Sulawesi, Indonesia | [25]          |
|                                | CH$_2$Cl$_2$ fraction of MeOH extract | -        | -            | Sheraton Caverns, Kauai, Hawaii                     | [26]          |
|                                | Et$_2$O fraction of acetone extract   | -        | -            | Xisha Island, Hainan, China                         | [27]          |
| 5-(-)-Epi-Ilimaquinone (2)     | CH$_2$Cl$_2$ fraction of MeOH extract | 358      | C$_{22}$H$_{30}$O$_4$ | * Similani island, Phuket, Thailand * Papua New Guinea | [16]          |
|                                | EtOAc fraction of MeOH extract        | -        | -            | Coral reef of Ishigaki Island, Okinawa, Japan      | [19]          |
|                                | CH$_2$Cl$_2$ fraction of MeOH extract | -        | -            | West Flores, Indonesia                              | [20]          |
|                                | 90% and 100% MeOH fraction of RP-18 CC/MeOH extract | -        | -            | Pugh Shoal, northeast of Truant Island, Australia   | [22]          |
Table 2. Cont.

| Compound Name                                      | Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country                        | Ref. |
|----------------------------------------------------|------------------|----------|--------------|--------------------------------------|------|
| n-Hexane fraction of MeOH extract                  | -                | -        |              | Island of Ambon, Indonesia           | [28] |
| CH₂Cl₂ fraction of MeOH extract                    | -                | -        |              | Sheraton Caverns, Kauai, Hawaii      | [26] |
| Et₂O fraction of acetone extract                   | -                | -        |              | Xisha Island, Hainan, China          | [27] |
| (−)-5,8-Diepi-Ilimaquinone (3)                     | CH₂Cl₂ fraction of H₂O extract | 358 C₂₂H₃₀O₄ | * Coast of Malaysia * Coast of Palau | [23] |
| (−)-Dactyloquinone A (4)                          | EtOAc fraction of MeOH extract | 356 C₂₂H₂₈O₄ | Coral reef of Ishigaki Island, Okinawa, Japan | [29] |
| (−)-Dactyloquinone B (5)                          | EtOAc fraction of MeOH extract | -        |              | Coral reef of Ishigaki Island, Okinawa, Japan | [19] |
| (−)-Dactyloquinone C (7)                          | EtOAc fraction of MeOH extract | 356 C₂₂H₂₈O₄ | Coral reef of Ishigaki Island, Okinawa, Japan | [19] |
| (−)-Dactyloquinone D (8)                          | EtOAc fraction of MeOH extract | 356 C₂₂H₂₈O₄ | Coral reef of Ishigaki Island, Okinawa, Japan | [19] |
| (−)-Dactyloquinone E (9)                          | EtOAc fraction of MeOH extract | 356 C₂₂H₂₈O₄ | Coral reef of Ishigaki Island, Okinawa, Japan | [19] |
| (+)-Neo-dactyloquinone (10)                        | EtOAc fraction of MeOH extract | 356 C₂₂H₂₈O₄ | Coral reef of Ishigaki Island, Okinawa, Japan | [30] |
| (+)-Isospongiaquinone (11)                         | CH₂Cl₂ fraction of MeOH extract | 358 C₂₂H₃₀O₄ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| n-Hexane fraction of MeOH extract                  | -                | -        |              | Island of Ambon, Indonesia           | [28] |
| Bolinaquinone (12)                                 | CH₂Cl₂ fraction of MeOH extract | 358 C₂₂H₃₀O₄ | West Flores, Indonesia                | [24] |
| Dictyceratidaquinone (13)                          | EtOAc fraction of CH₂Cl₂ of MeOH extract | 358 C₂₂H₃₀O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia | [21] |
Table 2. Cont.

| Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country | Ref. |
|------------------|----------|--------------|---------------|------|
| Mamanuthaquinone (14) | EtOAc fraction of CH₂Cl₂ of MeOH extract | 358 | C₂₂H₃₀O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba (Australia), [21] |
| Hyatellaquinone (15) | EtOAc fraction of CH₂Cl₂ of MeOH extract | 358 | C₂₂H₃₀O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia [21] |
| (+)-Isohyatellaquinone (16) | EtOAc fraction of CH₂Cl₂ of MeOH extract | 358 | C₂₂H₃₀O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia [21] |
| (−)-Ent-Isohyatellaquinone (17) | EtOAc fraction of CH₂Cl₂ of MeOH extract | 358 | C₂₂H₃₀O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia [21] |
| Neomamanuthaquinone (18) | EtOAc fraction of CH₂Cl₂ of MeOH extract | 344 | C₂₁H₂₆O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia [21] |
| 7,8-Dehydrocyclospongiaquinone-2 (19) | EtOAc fraction of CH₂Cl₂ of MeOH extract | 356 | C₂₂H₂₆O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia [21] |
| 9-Epi-7,8-Dehydrocyclospongiaquinone-2 (20) | EtOAc fraction of CH₂Cl₂ of MeOH extract | 356 | C₂₂H₂₆O₄ | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia [21] |
| Cyclospongiaquinone-1 (21) | CH₂Cl₂ fraction of H₂O extract | 358 | C₂₂H₃₀O₄ | * Coast of Malaysia * Coast of Palau [23] |
| Cyclospongiaquinone-2 (22) | CH₂Cl₂ fraction of H₂O extract | 358 | C₂₂H₃₀O₄ | * Coast of Malaysia * Coast of Palau [23] |
| (−)-4,5-Diepi-Dactylospongiaquinone (23) | CH₂Cl₂ fraction of H₂O extract | 358 | C₂₂H₂₆O₄ | * Coast of Malaysia * Coast of Palau [23] |
| (−)-10,17-O-Cyclo-4,5-diepi-dactylospongiaquinone (24) | CH₂Cl₂ fraction of H₂O extract | 356 | C₂₂H₂₆O₄ | * Coast of Malaysia * Coast of Palau [23] |
| Smenospongine (25) | CH₂Cl₂ fraction of MeOH extract | 343 | C₂₁H₂₉NO₃ | * Similani island, Phuket, Thailand * Papua New Guinea [16] |
| Smenospongine (26) | CH₂Cl₂ fraction of MeOH extract | - | - | West Flores, Indonesia [20] |
| Smenospongine (26) | CH₂Cl₂ fraction of MeOH extract | - | - | West Flores, Indonesia [31] |
| Smenospongine (26) | CH₂Cl₂ fraction of MeOH extract | - | - | West Flores, Indonesia [24] |
| Smenospongine (26) | RP-18 CC, 60% MeOH/H₂O of MeOH extract | - | - | Towo’e Beach Tahuna Bay, Sangihe Islands North Sulawesi, Indonesia [25] |
| Smenospongine (26) | CH₂Cl₂ fraction of MeOH extract | - | - | Sheraton Caverns, Kauai, Hawaii [26] |
| 5-(+)-Epi-Smenospongine (26) | CH₂Cl₂ fraction of MeOH extract | 343 | C₂₁H₂₉NO₃ | West Flores, Indonesia [20] |
### Table 2. Cont.

The Chemical Structures of Compounds 1–12 (Figure 1), 13–24 (Figure 2), 25–36 (Figure 3), 37–48 (Figure 4), 49–60 (Figure 5), 61–70 (Figure 6), 71–80 (Figure 7), 81–91 (Figure 8), and 92–101 (Figure 9) are illustrated. Compound Name

| Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country | Ref. |
|------------------|----------|--------------|---------------|------|
| CH₂Cl₂ fraction of MeOH extract | - | - | West Flores, Indonesia | [24] |
| CH₂Cl₂/MeOH fractions of EtOH extract | 357 | C_{22}H_{31}NO₃ | Yongxing Island, South China Sea | [32] |
| 90% and 100% MeOH fraction of RP-18 CC of MeOH extract | 401 | C_{23}H_{31}NO₃ | Pugh Shoal, northeast of Truant Island, Australia | [22] |
| 90% and 100% MeOH fraction of RP-18 CC of MeOH extract | 415 | C_{24}H_{33}NO₃ | Pugh Shoal, northeast of Truant Island, Australia | [22] |
| CH₂Cl₂/MeOH fraction of EtOH extract | - | - | Island of Ambon, Indonesia | [28] |
| CH₂Cl₂ fraction of MeOH extract | 399 | C_{25}H_{37}NO₃ | West Flores, Indonesia | [20] |
| CH₂Cl₂/MeOH fraction of EtOH extract | - | - | Sheraton Caverns, Kauai, Hawaii | [26] |
| CH₂Cl₂/MeOH fraction of EtOH extract | - | - | Yongxing Island, South China Sea | [32] |
| CH₂Cl₂ fraction of MeOH extract | 399 | C_{25}H_{37}NO₃ | West Flores, Indonesia | [20] |
| CH₂Cl₂ fraction of MeOH extract | - | - | West Flores, Indonesia | [24] |
| CH₂Cl₂ fraction of MeOH extract | - | - | West Flores, Indonesia | [24] |
| CH₂Cl₂ fraction of MeOH extract | - | - | Sheraton Caverns, Kauai, Hawaii | [26] |
| CH₂Cl₂ fraction of MeOH extract | - | - | Yongxing Island, South China Sea | [32] |
| CH₂Cl₂ fraction of MeOH extract | 413 | C_{26}H_{39}NO₃ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| CH₂Cl₂/MeOH fraction of EtOH extract | - | - | Yongxing Island, South China Sea | [32] |
| CH₂Cl₂ fraction of MeOH extract | 413 | C_{26}H_{39}NO₃ | * Similani island, Phuket, Thailand * Papua New Guinea | [15] |
| CH₂Cl₂/MeOH fraction of EtOH extract | - | - | Sheraton Caverns, Kauai, Hawaii | [26] |
| CH₂Cl₂ fraction of MeOH extract | 445 | C_{25}H_{35}NO₆ | Island of Ambon, Indonesia | [28] |
| CH₂Cl₂ fraction of MeOH extract | 447 | C_{29}H_{37}NO₃ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| CH₂Cl₂ fraction of MeOH extract | - | - | West Flores, Indonesia | [20] |
| CH₂Cl₂ fraction of MeOH extract | - | - | Sheraton Caverns, Kauai, Hawaii | [26] |
| CH₂Cl₂ fraction of MeOH extract | 447 | C_{29}H_{37}NO₃ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
Table 2. Cont.

| Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country | Ref. |
|------------------|----------|--------------|---------------|------|
| CH$_2$Cl$_2$ fraction of MeOH extract | - | - | West Flores, Indonesia | [20] |
| CH$_2$Cl$_2$ fraction of MeOH extract | - | - | West Flores, Indonesia | [24] |
| n-Hexane fraction of MeOH extract | - | - | Island of Ambon, Indonesia | [28] |
| Nakijiquinone V (37) | RP-18 CC, 60% MeOH/H$_2$O of MeOH extract | 437 | C$_{26}$H$_{35}$N$_3$O$_3$ | Towo’e Beach Tahuna Bay, Sangihe Islands, North Sulawesi, Indonesia | [25] |
| Dysideamine (38) | CH$_2$Cl$_2$ fraction of MeOH extract | 343 | C$_{21}$H$_{29}$NO$_3$ | West Flores, Indonesia | [24] |
| Isosmenospongine (39) | n-Hexane fraction of MeOH extract | 343 | C$_{21}$H$_{29}$NO$_3$ | Island of Ambon, Indonesia | [28] |
| Nakijiquinone A (40) | n-Hexane fraction of MeOH extract | 401 | C$_{23}$H$_{31}$NO$_5$ | Island of Ambon, Indonesia | [28] |
| Nakijiquinone B (41) | n-Hexane fraction of MeOH extract | 443 | C$_{26}$H$_{37}$NO$_3$ | Island of Ambon, Indonesia | [28] |
| Nakijiquinone C (42) | n-Hexane fraction of MeOH extract | 431 | C$_{24}$H$_{33}$NO$_6$ | Island of Ambon, Indonesia | [28] |
| Nakijiquinone G (43) | n-Hexane fraction of MeOH extract | 437 | C$_{26}$H$_{35}$N$_3$O$_3$ | Island of Ambon, Indonesia | [28] |
| 5-Epi-Nakijiquinone Q (44) | n-Hexane fraction of MeOH extract | 447 | C$_{29}$H$_{37}$NO$_3$ | Island of Ambon, Indonesia | [28] |
| 20-Demethoxy-20-methylaminodactyloquinone D (45) | CH$_2$Cl$_2$/MeOH fraction of EtOH extract | 355 | C$_{22}$H$_{29}$NO$_3$ | Yongxing Island, South China Sea | [32] |
| 20-Demethoxy-20-isobutylaminodactyloquinone D (46) | CH$_2$Cl$_2$/MeOH fraction of EtOH extract | 397 | C$_{25}$H$_{35}$NO$_3$ | Yongxing Island, South China Sea | [32] |
| 20-Demethoxy-20-isopentylaminodactyloquinone D (47) | CH$_2$Cl$_2$/MeOH fraction of EtOH extract | 411 | C$_{26}$H$_{37}$NO$_3$ | Yongxing Island, South China Sea | [32] |
| (+)-Smenospondiol (48) | CH$_2$Cl$_2$ fraction of MeOH extract | 372 | C$_{23}$H$_{32}$O$_4$ | * Similani island, Phuket, Thailand + Papua New Guinea | [16] |
| (+)-Dictyoceratin A (49) | CH$_2$Cl$_2$ fraction of MeOH extract | 372 | C$_{23}$H$_{32}$O$_4$ | * Similani island, Phuket, Thailand + Papua New Guinea | [16] |
| n-Hexane fraction of MeOH extract | - | - | Sheraton Caverns, Kauai, Hawaii | [26] |
| Et$_2$O fraction of acetone extract | - | - | Xisha Island, Hainan, China | [27] |
| 19-Methoxy-dictyoceratin-A (50) | CH$_2$Cl$_2$/MeOH fractions of EtOH extract | 402 | C$_{24}$H$_{34}$O$_3$ | Yongxing Island, South China Sea | [32] |
| (+)-Dictyoceratin B (51) | n-Hexane fraction of MeOH extract | 388 | C$_{22}$H$_{32}$O$_3$ | Sheraton Caverns, Kauai, Hawaii | [26] |
| Compound Name          | Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country               | Ref.          |
|------------------------|------------------|----------|--------------|-----------------------------|--------------|
| Et$_2$O fraction of acetone extract | - | - | Xisha Island, Hainan, China | [27]        |
| (+)-Dictyoceratin C (52) | CH$_2$Cl$_2$ fraction of MeOH extract | 356 | C$_{23}$H$_{32}$O$_3$ | Pulan Tiga, Sabah, Malaysia | [17]        |
| CH$_2$Cl$_2$ fraction of MeOH extract | - | - | West Flores, Indonesia | [20]        |
| CH$_2$Cl$_2$ fraction of MeOH extract | - | - | West Flores, Indonesia | [24]        |
| EtOAc fraction of EtOH extract | - | - | Meishan coral reef, Sanya, China | [33]        |
| RP-18 CC, 60% MeOH/H$_2$O of MeOH extract | - | - | Towo’e Beach Tahuna Bay, Sangihe Islands North Sulawesi, Indonesia | [25]        |
| n-Hexane fraction of MeOH extract | - | - | Sheraton Caverns, Kauai, Hawaii | [26]        |
| CH$_2$Cl$_2$/MeOH fraction of EtOH extract | - | - | Yongxing Island, South China Sea | [32]        |
| Et$_2$O fraction of acetone extract | - | - | Xisha Island, Hainan, China | [27]        |
| Polyfibrospongol A (53) | EtOAc fraction of EtOH extract | 386 | C$_{24}$H$_{34}$O$_4$ | Meishan coral reef, Sanya, China | [33]        |
| Et$_2$O fraction of acetone extract | - | - | Xisha Island, Hainan, China | [27]        |
| (−)-Xishaeleganin C (54) | Et$_2$O fraction of acetone extract | 372 | C$_{23}$H$_{32}$O$_4$ | Xisha Island, Hainan, China | [27]        |
| (+)-Xishaeleganin D (55) | Et$_2$O fraction of acetone extract | 356 | C$_{23}$H$_{32}$O$_3$ | Xisha Island, Hainan, China | [27]        |
| (−)-Xishaeleganin A (56) | Et$_2$O fraction of acetone extract | 386 | C$_{24}$H$_{34}$O$_4$ | Xisha Island, Hainan, China | [27]        |
| (−)-Xishaeleganin B (57) | Et$_2$O fraction of acetone extract | 390 | C$_{23}$H$_{34}$O$_3$ | Xisha Island, Hainan, China | [27]        |
| (−)-Smenodiol (58) | CH$_2$Cl$_2$ fraction of MeOH extract | 372 | C$_{23}$H$_{32}$O$_4$ | * Similani island, Phuket, Thailand, * Papua New Guinea | [16]        |
| CH$_2$Cl$_2$ fraction of MeOH extract | - | - | Pelorus Island, the Great Barrier Reef, Queensland, Australia | [18]        |
| (−)-Dactylosponon (59) | CH$_2$Cl$_2$ fraction of MeOH extract | 356 | C$_{23}$H$_{32}$O$_3$ | * Similani island, Phuket, Thailand, * Papua New Guinea | [16]        |
| (−)-Dactylospontriol (60) | CH$_2$Cl$_2$ fraction of MeOH extract | 388 | C$_{23}$H$_{32}$O$_3$ | * Similani island, Phuket, Thailand, * Papua New Guinea | [16]        |
| (+)-Cyclospongiacatechol (61) | CH$_2$Cl$_2$ fraction of H$_2$O extract | 388 | C$_{23}$H$_{32}$O$_3$ | * Coast of Malaysia, * Coast of Palau | [23]        |
| Chromazonarol (62) | CH$_2$Cl$_2$ fraction of MeOH extract | 314 | C$_{21}$H$_{30}$O$_2$ | * Similani island, Phuket, Thailand, * Papua New Guinea | [16]        |
Table 2. Cont.

| Compound Name                                | Extract/Fraction                   | Mol. Wt. | Mol. Formula | City, Country                        | Ref.                 |
|----------------------------------------------|------------------------------------|----------|--------------|--------------------------------------|----------------------|
| 8-Epi-Chromazonarol (63)                     | CH₂Cl₂ fraction of MeOH extract    | 314      | C₂₁H₃₀O₂    | * Similani island, Phuket, Thailand  | [16]                 |
|                                              |                                    |          |              | * Papua New Guinea                   |                      |
|                                              | CH₂Cl₂ fraction of H₂O extract     | -        | -            | * Coast of Malaysia                  | [23]                 |
|                                              |                                    |          |              | * Coast of Palau                     |                      |
| Pelorol (64)                                 | CH₂Cl₂ fraction of MeOH extract    | 372      | C₂₃H₃₂O₄    | Pelorus Island, the Great Barrier Reef, Queensland, Australia | [18]                 |
|                                              | n-Hexane fraction of MeOH extract  | -        | -            | Island of Ambon, Indonesia           | [28]                 |
| Nakijinol B (65)                             | 90% and 100% MeOH fraction of RP-18 CC of MeOH extract | 355 | C₂₂H₂₉NO₃ | Pugh Shoal, northeast of Truant Island, Australia | [22]                 |
| Popolohuanone B (66)                         | CH₂Cl₂ fraction of CH₂Cl₂/MeOH extract | 623 | C₂₂H₃₇NO₃ | Xisha Islands maritime space, South China Sea | [34]                 |
| Popolohuanone C (67)                         | CH₂Cl₂ fraction of CH₂Cl₂/MeOH extract | 623 | C₂₂H₃₇NO₃ | Xisha Islands maritime space, South China Sea | [34]                 |
| Popolohuanone G (68)                         | CH₂Cl₂ fraction of CH₂Cl₂/MeOH extract | 642 | C₂₂H₳₃₆O₄ | Xisha Islands maritime space, South China Sea | [34]                 |
| Popolohuanone H (69)                         | CH₂Cl₂ fraction of CH₂Cl₂/MeOH extract | 623 | C₂₂H₳₃₇NO₃ | Xisha Islands maritime space, South China Sea | [34]                 |
| Popolohuanone I (70)                         | CH₂Cl₂ fraction of CH₂Cl₂/MeOH extract | 623 | C₂₂H₳₃₇NO₃ | Xisha Islands maritime space, South China Sea | [34]                 |
| (−)-Dactyltronic acid A (71)                 | CH₂Cl₂ fraction of MeOH extract    | 362      | C₂₁H₳₃₀O₅ | Pulan Tiga, Sabah, Malaysia           | [17]                 |
|                                              | EtOAc fraction of EtOH extract     | -        | -            | Meishan coral reef, Sanya, China     | [33]                 |
| (−)-Dactyltronic acid B (72)                 | CH₂Cl₂ fraction of MeOH extract    | 362      | C₂₁H₳₃₀O₅ | Pulan Tiga, Sabah, Malaysia           | [17]                 |
|                                              | EtOAc fraction of EtOH extract     | -        | -            | Meishan coral reef, Sanya, China     | [33]                 |
| (+)-Dactylolactone A (73)                    | EtOAc fraction of MeOH extract     | 404      | C₂₂H₳₃₂O₆ | Coral reef of Ishigaki Island, Okinawa, Japan | [30]                 |
| (+)-Dactylolactone B (74)                    | EtOAc fraction of MeOH extract     | 404      | C₂₂H₳₃₂O₆ | Coral reef of Ishigaki Island, Okinawa, Japan | [30]                 |
| (+)-Dactylolactone C (75)                    | EtOAc fraction of MeOH extract     | 404      | C₂₂H₳₃₂O₆ | Coral reef of Ishigaki Island, Okinawa, Japan | [30]                 |
| (+)-Dactylolactone D (76)                    | EtOAc fraction of MeOH extract     | 404      | C₂₂H₳₃₂O₆ | Coral reef of Ishigaki Island, Okinawa, Japan | [30]                 |
| (+)-Dactylospene B (77)                      | CH₂Cl₂/MeOH fraction of EtOH extract | 400 | C₂₈H₄₆O₃ | Yongxing Island, South China Sea      | [35]                 |
| (+)-Dactylospene C (78)                      | CH₂Cl₂/MeOH fraction of EtOH extract | 400 | C₂₈H₄₆O₃ | Yongxing Island, South China Sea      | [35]                 |
Table 2. Cont.

The Chemical Structures of Compounds 1–12 (Figure 1), 13–24 (Figure 2), 25–36 (Figure 3), 37–48 (Figure 4), 49–60 (Figure 5), 61–70 (Figure 6), 71–80 (Figure 7), 81–91 (Figure 8), and 92–101 (Figure 9) are illustrated. Compound Name

| Compound Name | Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country | Ref. |
|---------------|-----------------|----------|--------------|---------------|-----|
| (+)-Dactylospene D (79) | CH$_2$Cl$_2$/MeOH fraction of EtOH extract | 432 | C$_{27}$H$_{44}$O$_4$ | Yongxing Island, South China Sea | [35] |
| (+)-Dactylospene E (80) | CH$_2$Cl$_2$/MeOH fraction of EtOH extract | 432 | C$_{27}$H$_{44}$O$_4$ | Yongxing Island, South China Sea | [35] |
| Dactylospongenone A (81) | CH$_2$Cl$_2$ fraction of MeOH extract | 390 | C$_{23}$H$_{34}$O$_5$ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| Dactylospongenone B (82) | CH$_2$Cl$_2$ fraction of MeOH extract | 390 | C$_{23}$H$_{34}$O$_5$ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| Dactylospongenone C (83) | CH$_2$Cl$_2$ fraction of MeOH extract | 390 | C$_{23}$H$_{34}$O$_5$ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| Dactylospongenone D (84) | CH$_2$Cl$_2$ fraction of MeOH extract | 390 | C$_{23}$H$_{34}$O$_5$ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| Dactylospongenone G (85) | n-Hexane fraction of MeOH extract | 404 | C$_{22}$H$_{32}$O$_6$ | Island of Ambon, Indonesia | [28] |
| Dactylospongenone H (86) | n-Hexane fraction of MeOH extract | 390 | C$_{22}$H$_{34}$O$_5$ | Island of Ambon, Indonesia | [28] |
| (−)-Smenospongic acid (87) | CH$_2$Cl$_2$ fraction of MeOH extract | 250 | C$_{16}$H$_{26}$O$_2$ | * Similani island, Phuket, Thailand * Papua New Guinea | [16] |
| (+)-Eleganstone A (88) | CH$_2$Cl$_2$ fraction of EtOH extract | 404 | C$_{24}$H$_{38}$O$_3$ | Yongxing Island and Seven Connected Islets, South China Sea | [36] |
| Diacetoxydolabella-2,7-dien-6-one (89) | CH$_2$Cl$_2$ fraction of EtOH extract | 404 | C$_{24}$H$_{38}$O$_3$ | Yongxing Island and Seven Connected Islets, South China Sea | [36] |
| (+)-(1R*,2E,4R*,8E,10S*,11S*,12R*)-10,18-Diacetoxydolabella-2,8-dien-6-one (90) | CH$_2$Cl$_2$ fraction of EtOH extract | 404 | C$_{24}$H$_{38}$O$_3$ | Yongxing Island and Seven Connected Islets, South China Sea | [36] |
| (1R*,2E,4R*,7Z,10S*,11S*,12R*)-10,18-Diacetoxydolabella-2,7-dien-6-one (91) | CH$_2$Cl$_2$ fraction of EtOH extract | 404 | C$_{24}$H$_{38}$O$_3$ | Yongxing Island and Seven Connected Islets, South China Sea | [36] |
| Furospinosulin-1 (92) | EtOAc fraction of CH$_2$Cl$_2$ of MeOH extract | 354 | C$_{25}$H$_{38}$O | Coral Gardens dive site at the Inner Gneerings reef, a group of shoals near Mooloolaba, Australia | [21] |
### Table 2. Cont.

| Compound Name | Extract/Fraction | Mol. Wt. | Mol. Formula | City, Country | Ref. |
|---------------|------------------|----------|--------------|---------------|------|
| Furospinosulin B (93) | CH\(_2\)Cl/MeOH fractions of EtOH extract | 370 | C\(_{25}\)H\(_{36}\)O\(_2\) | Yongxing Island, South China Sea | [35] |
| (−)-Luffariellolide (94) | CH\(_2\)Cl/MeOH fractions of EtOH extract | 386 | C\(_{25}\)H\(_{36}\)O\(_3\) | Yongxing Island, South China Sea | [35] |
| (−)-Dactylospene A (95) | CH\(_2\)Cl/MeOH fractions of EtOH extract | 386 | C\(_{25}\)H\(_{36}\)O\(_3\) | Yongxing Island, South China Sea | [35] |
| Pregna-1,20-dien-3-one (96) | EtOAc fraction of EtOH extract | 298 | C\(_{21}\)H\(_{30}\)O | Meishan coral reef, Sanya, China | [33] |
| 3-Hydroxycholesta-5,8-dien-7-one (97) | EtOAc fraction of EtOH extract | 398 | C\(_{27}\)H\(_{42}\)O | Meishan coral reef, Sanya, China | [33] |
| (35,5R,9R,10S,13R,17R,20R,24S,22E)-Ergosta-6,8,22-triene-3,25-diol (98) | CH\(_2\)Cl/MeOH extract | 412 | C\(_{28}\)H\(_{42}\)O\(_2\) | Xisha islands maritime space, South China Sea | [37] |
| (35,5R,9R,10S,13R,17R,20R,24S,22E)-Ergosta-6,8,22-triene-25-ol-3-sulfonate (99) | CH\(_2\)Cl/MeOH extract | 492 | C\(_{28}\)H\(_{42}\)O\(_3\)S | Xisha islands maritime space, South China Sea | [37] |
| 5α,8α-Epidioxy-cholest-6-en-3β-ol (100) | CH\(_2\)Cl/MeOH extract | 416 | C\(_{27}\)H\(_{42}\)O\(_3\) | Xisha islands maritime space, South China Sea | [37] |
| Kauamide (101) | n-Hexane fraction of MeOH extract | 357 | C\(_{19}\)H\(_{33}\)ClNO\(_3\) | Sheraton Caverns, Kauai, Hawaii | [25] |

* Compound isolated from sponge’s sample obtained from two different locations in the same study.

#### 2.1. Sesquiterpenes

2.1.1. Sesquiterpenic Quinones/Hydroquinones

Sesquiterpenic quinones/hydroquinones are a class of natural marine metabolites that are mainly reported from order Dictyoceratida sponges, including various genera such as *Dysidea*, *Fenestraspongia*, *Hyrtios*, *Dactylospongia*, *Petrosaspongia*, *Spongia*, and *Hippospongia* [27,32]. They can be either with the drimane or rearranged drimane (clerodane-decalin or 4,9-friedodrimane) skeleton, having four stereo-genic centers. The quinone/hydroquinone moiety could be mono, di, tri, tetra, or penta-substituted. These substituents can be hydroxy, methoxy, methyl ester, or amino groups. These metabolites possess variable structures based on the configuration at C-5 (cis- or trans-clerodane skeleton), C-9, C-8 and/or the position of the double bond. These metabolites have drawn remarkable interest due to their diverse structures and bioactivities.

Cancer represents one of the main reasons for death that has the second-highest incidence of mortality after cardiovascular diseases [38]. Chemotherapeutic treatment is the most common strategy for cancer treatment. However, the chemotherapeutic agents influence not only tumor cells but also normal cells resulting in hazardous side effects [39]. *D. elegans* reported sesquiterpenes have been evaluated for their anticancer potential towards various cancer cell lines. Further, some studies reported the structure–activity relationship and synthesis of some analogs have been discussed as shown here.

In 2017, Boufridi et al. assayed cytotoxic and apoptotic potential of (−)-ilimaquinone (1) and 5-(+)-epi-ilimaquinone (2) using Cell Titer-Glo luminescent cell viability assay towards HeLa (cervical adenocarcinoma), PC3 (prostate adenocarcinoma), MES-SA (uterine sarcoma), and MESSA/D×5 (multidrug-resistant uterine sarcoma) (Figure 1). These metabolites 1 and 2 possessed more potent growth inhibitory capacities against MES-SA
and MESSA/D×5 (IC\textsubscript{50} values of 2.44 and 2.56 µM for MES-SA and 10.48 and 12.54 µM, respectively, for MESSA/D×5). The incubation of MES-SA and MES-SA/D×5 cells with 5 and 50 µM of both 1 and 2 resulted in significant elevated caspases proteolytic activity in both cell lines, revealing the apoptotic capacity of both compounds. It is noteworthy that ilimaquinone had more potent cytotoxic and apoptotic potential than its C-5 epimer [40].

The new sesquiterpene quinones; (+)-isohyatellaquinone (16), (−)-ent-isohyatellaquinone (17), 7,8-dehydrocyclospongiaquinone-2 (19), and 9-epi-7,8-dehydrocyclospongiaquinone-2 (20), in addition to the known sesquiterpenes; 1, 13, 14, and 15 were separated and purified from CH\textsubscript{2}Cl\textsubscript{2}/MeOH extract using AgNO\textsubscript{3} (silver nitrate) flash chromatography (FC) and AgNO\textsubscript{3}-impregnated TLC (Figure 2). AgNO\textsubscript{3} FC is an appropriate technique for the separation of metabolites with a difference in the alkene substitution pattern. Their relative configuration was assigned based on NOESY and optical rotation analyses. These compounds were identified by different spectroscopic techniques. Compound 13 featured an uncommon cyclopropyl moiety and trans-C-10 and C-5 ring junction, whereas 16 having drimane moiety linked to OH-substituted quinone, was structurally similar to 15 with an opposite optical rotation sign. On the other side, 19 is a dehydro-derivative of cyclospongiaquinone-2 (22), having a C-9-spiro center, while 20 differed from 19 in C-9-stereochemistry [21]. In cytotoxicity test, 1, 14, and 15 had potent potential (IC\textsubscript{50} ranging from 1.50 to 4.45 µg/mL), compared to doxorubicin (IC\textsubscript{50} 0.29 µg/mL) versus the BC cell line whereas 16 and 20 demonstrated moderate capacity (IC\textsubscript{50} 6.69 and 7.38 µg/mL, respectively) in the MTT method. Only 1 (IC\textsubscript{50} 3.37 µg/mL) possessed a strong potential versus NCI-H187 cell line in comparison to doxorubicin (IC\textsubscript{50} 0.06 µg/mL) (Table 3).

Table 3. Biological activity of reported metabolites from Dactylospongia elegans.

| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Ref. |
|---------------|---------------------|------------------------------|-------------------|-----|
| (−)-Ilimaquinone (1) | Antitrypanosomal | Semiautomated microdilution/Trypanosoma brucei | 7.7 µg/mL (IC\textsubscript{50}) | Melsaroprol 0.0026 µg/mL (IC\textsubscript{50}) | [18] |
| | Antimalarial | Semiautomated microdilution/P. falciparum clone K1 | 1743.0 µg/mL (IC\textsubscript{50}) | Chloroquine 91.0 µg/mL (IC\textsubscript{50}) | [18] |
| | | Semiautomated microdilution/P. falciparum clone NF54 | 949.0 µg/mL (IC\textsubscript{50}) | Chloroquine 4.6 µg/mL (IC\textsubscript{50}) | [18] |
| | Cytotoxicity | MTT/BC | 1.50 µg/mL (IC\textsubscript{50}) | Doxorubicin 0.29 µg/mL (IC\textsubscript{50}) | [21] |
| | | MTT/NCI-H187 | 3.37 µg/mL (IC\textsubscript{50}) | Doxorubicin 0.06 µg/mL (IC\textsubscript{50}) | [21] |
| | | SRB/SF-268 | 2.7 µM (GI\textsubscript{50}) | Vehicle-DMSO | [22] |
| | | SRB/MCF-7 | 3.9 µM (GI\textsubscript{50}) | Vehicle-DMSO | [22] |
| | | SRB/H460 | 1.8 µM (GI\textsubscript{50}) | Vehicle-DMSO | [22] |
| | | SRB/HT-29 | 5.4 µM (GI\textsubscript{50}) | Vehicle-DMSO | [22] |
| | | SRB/CHO-K1 | 2.0 µM (GI\textsubscript{50}) | Vehicle-DMSO | [22] |
| | β-Secretase 1 inhibition | BACE1 | 65.0 µM (IC\textsubscript{50}) | - | [26] |
| | Cytotoxicity | MTT/U251 | 19.3 µM (CC\textsubscript{50}) | Vehicle-DMSO | [26] |
| | | MTT/Panc-1 | 20.4 µM (CC\textsubscript{50}) | Vehicle-DMSO | [26] |
| | Antibacterial | Broth microdilution/S. aureus USA300 LAC | 5.6 µg/mL (MIC) | Vancomycin 1.0 µg/mL (MIC) | [27] |
| | | Broth microdilution/S. pyogenes ATCC 12344 | 2.8 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
| | | Broth microdilution/E. faecium Efum-HS0649 | 11.2 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
Table 3. Cont.

| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Ref. |
|---------------|---------------------|-------------------------------|--------------------|------|
| 5-(-)-Epi-Ilimaqinone (2) | Cytotoxicity | A549 | 0.9 µg/mL (IC₅₀) | - | [16] |
| | | HT-29 | 3.4 µg/mL (IC₅₀) | - | [16] |
| | | B₁₅F₁₀ | 1.1 µg/mL (IC₅₀) | - | [16] |
| | | P388 | 2.2 µg/mL (IC₅₀) | - | [16] |
| | Cytotoxicity | MTT/L5178Y | 2.23 µM (IC₅₀) | Kahalalide F 4.30 µM (IC₅₀) | [28] |
| | Antibacterial | Broth microdilution/ S. aureus ATCC 2923 | 50.0 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
| | | Broth microdilution/ S. aureus ATCC 700699 | 50.0 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
| | | Cytotoxicity | MTT/U251 | 19.4 µM (CC₅₀) | Vehicle-DMSO | [26] |
| | | MTT/Panc-1 | 16.2 µM (CC₅₀) | Vehicle-DMSO | [26] |
| | Antibacterial | Broth microdilution / S. aureus USA300 LAC | 5.6 µg/mL (MIC) | Vancomycin 1.0 µg/mL (MIC) | [27] |
| | | Broth microdilution/ S. pyogenes ATCC 12344 | 2.8 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
| | | Broth microdilution/ E. faecium Efm-HS0649 | 11.2 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
| (−)-Dactyloquinone A (4) | Antibacterial | Broth microdilution / S. pyogenes ATCC 12344 | 44.5 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
| | | Broth microdilution/ E. faecium Efm-HS0649 | 22.2 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
| (−)-Dactyloquinone B (5) | Cytotoxicity | SRB/SF-268 | 32.0 µM (GI₅₀) | Vehicle-DMSO | [22] |
| | | SRB/MCF-7 | 41.0 µM (GI₅₀) | Vehicle-DMSO | [22] |
| | | SRB/H460 | 30.0 µM (GI₅₀) | Vehicle-DMSO | [22] |
| | | SRB/HT-29 | 46.0 µM (GI₅₀) | Vehicle-DMSO | [22] |
| | | SRB/CHO-K1 | 43.0 µM (GI₅₀) | Vehicle-DMSO | [22] |
| | Antibacterial | Broth microdilution/ S. aureus USA300 LAC | 178.0 µg/mL (MIC) | Vancomycin 1.0 µg/mL (MIC) | [27] |
| | | Broth microdilution/ S. pyogenes ATCC 12344 | 22.2 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
| | | Broth microdilution/ E. faecium Efm-HS0649 | 22.2 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
| (−)-Dactyloquinone C (7) | Antibacterial | Broth microdilution/ S. aureus USA300 LAC | 11.1 µg/mL (MIC) | Vancomycin 1.0 µg/mL (MIC) | [27] |
| | | Broth microdilution/ S. pyogenes ATCC 12344 | 5.6 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
| | | Broth microdilution/ E. faecium Efm-HS0649 | 5.6 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
| (−)-Dactyloquinone D (8) | Antibacterial | Broth microdilution/ S. pyogenes ATCC 12344 | 89.0 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
| | | Broth microdilution/ E. faecium Efm-HS0649 | 178.0 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
| (+)-Dactyloquinone E (9) | Antibacterial | Broth microdilution/ S. pyogenes ATCC 12344 | 22.2 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
| | | Broth microdilution/ E. faecium Efm-HS0649 | 178.0 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
Table 3. Cont.

| Compound Name                          | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Ref. |
|----------------------------------------|---------------------|------------------------------|--------------------|------|
| (+)-Isospongiaquinone (11)             | Cytotoxicity        | MTT/L5178Y                   | 1.34 µM (IC50)     |      |
|                                        |                     |                              | Kahalalide F 4.30 µM (IC50) | [28] |
|                                        |                      |                              | Broth microdilution/S. aureus ATCC 25923 50.0 µM (MIC) | [28] |
|                                        |                      |                              | Broth microdilution/S. aureus ATCC 700699 50.0 µM (MIC) | [28] |
|                                        |                      |                              | Broth microdilution/E. faecalis ATCC 51299 50.0 µM (MIC) | [28] |
|                                        |                      |                              | Broth microdilution/E. faecalis ATCC 35677 50.0 µM (MIC) | [28] |
|                                        |                      |                              | Broth microdilution/E. faecalis ATCC 700221 50.0 µM (MIC) | [28] |
| Mamanuthaquinone (14)                  | Cytotoxicity        | MTT/BC                       | 2.61 µg/mL (IC50)  |      |
|                                        |                      |                              | Doxorubicin 0.29 µg/mL (IC50) | [21] |
|                                        |                      | MTT/NCI-H187                 | 8.78 µg/mL (IC50)  |      |
|                                        |                      |                              | Doxorubicin 0.06 µg/mL (IC50) | [21] |
| Hyatellaquinone (15)                   | Cytotoxicity        | MTT/BC                       | 4.45 µg/mL (IC50)  |      |
|                                        |                      |                              | Doxorubicin 0.29 µg/mL (IC50) | [21] |
|                                        |                      | MTT/NCI-H187                 | 10.90 µg/mL (IC50) |      |
|                                        |                      |                              | Doxorubicin 0.06 µg/mL (IC50) | [21] |
|                                        |                      | MTT/BC                       | 1.50 µg/mL (IC50)  |      |
|                                        |                      |                              | Doxorubicin 0.29 µg/mL (IC50) | [21] |
| (+)-Isohyatellaquinone (16)            | Cytotoxicity        | MTT/BC                       | 6.69 µg/mL (IC50)  |      |
|                                        |                      |                              | Doxorubicin 0.29 µg/mL (IC50) | [21] |
|                                        |                      | MTT/NCI-H187                 | 11.52 µg/mL (IC50) |      |
|                                        |                      |                              | Doxorubicin 0.06 µg/mL (IC50) | [21] |
| Neomamanuthaquinone (18)               | Cytotoxicity        | MTT/BC                       | 8.42 µg/mL (IC50)  |      |
|                                        |                      |                              | Doxorubicin 0.29 µg/mL (IC50) | [21] |
| 9-Epi-7,8-Dehydrocyclospongiaquinone-2 (20) | Cytotoxicity  | MTT/BC                       | 7.38 µg/mL (IC50)  |      |
|                                        |                      |                              | Doxorubicin 0.29 µg/mL (IC50) | [21] |
|                                        |                      | MTT/NCI-H187                 | 12.40 µg/mL (IC50) |      |
|                                        |                      |                              | Doxorubicin 0.06 µg/mL (IC50) | [21] |
| Smenospongine (25)                     | Cytotoxicity        | A549                         | 5.7 µg/mL (IC50)   | -    |
|                                        |                      | HT-29                        | 4.0 µg/mL (IC50)   | -    |
|                                        |                      | B16F10                       | 4.1 µg/mL (IC50)   | -    |
|                                        |                      | P388                         | 2.6 µg/mL (IC50)   | -    |
|                                        |                      | MTT/U251                     | 2.4 µM (CC50)      | Vehicle-DMSO | [26] |
| β-Secretase 1 inhibition               |                     | BACE1                        | 65.0 µM (IC50)     | -    |
| Smenospongimine (27)                   | Cytotoxicity        | CCK-8/DU145                  | 3.5 µM (IC50)      | Cisplatin 2.9 µM (IC50) | [32] |
|                                        |                      | CCK-8/SW1990                 | 4.2 µM (IC50)      | Cisplatin 1.2 µM (IC50) | [32] |
|                                        |                      | CCK-8/Huh7                   | 2.3 µM (IC50)      | Cisplatin 2.2 µM (IC50) | [32] |
|                                        |                      | CCK-8/Panc-1                 | 5.8 µM (IC50)      | Cisplatin 4.6 µM (IC50) | [32] |
| Smenospongine B (28)                   | Cytotoxicity        | SRB/SF-268                   | 9.7 µM (GI50)      | Vehicle-DMSO | [22] |
|                                        |                      | SRB/MCF-7                    | 10.0 µM (GI50)     | Vehicle-DMSO | [22] |
|                                        |                      | SRB/H460                     | 6.0 µM (GI50)      | Vehicle-DMSO | [22] |
| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Ref. |
|---------------|---------------------|------------------------------|--------------------|------|
| **SRB/HT-29** | Cytotoxicity | SRB/SF-268 | 6.0 µM (GI₅₀) | Vehicle-DMSO [22] |
| **SRB/CHO-K1** | Cytotoxicity | SRB/MCF-7 | 3.0 µM (GI₅₀) | Vehicle-DMSO [22] |
| **Smenospongine C (29)** | Cytotoxicity | SRB/H460 | 14.0 µM (GI₅₀) | Vehicle-DMSO [22] |
| **SRB/HT-29** | Cytotoxicity | SRB/CHO-K1 | 18.0 µM (GI₅₀) | Vehicle-DMSO [22] |
| **Smenospongorine (30)** | Cytotoxicity | MTT/U251 | 19.4 µM (CC₅₀) | Vehicle-DMSO [26] |
| **Smenospongorine (30)** | Cytotoxicity | MTT/Panc-1 | 22.6 µM (CC₅₀) | Vehicle-DMSO [26] |
| **Smenospongiarine (32)** | Cytotoxicity | CCK-8/DU145 | 4.2 µM (IC₅₀) | Cisplatin 2.9 µM (IC₅₀) [32] |
| **Smenospongiarine (32)** | Cytotoxicity | CCK-8/SW1990 | 4.4 µM (IC₅₀) | Cisplatin 1.2 µM (IC₅₀) [32] |
| **Smenospongiarine (32)** | Cytotoxicity | CCK-8/Huh7 | 3.0 µM (IC₅₀) | Cisplatin 2.2 µM (IC₅₀) [32] |
| **Smenospongiarine (32)** | Cytotoxicity | CCK-8/Panc-1 | 7.7 µM (IC₅₀) | Cisplatin 4.6 µM (IC₅₀) [32] |
| **5-(+)-Epi-Smenospongiarine (33)** | Cytotoxicity | A549 | 0.8 µg/mL (IC₅₀) | - [16] |
| **5-(+)-Epi-Smenospongiarine (33)** | Cytotoxicity | HT-29 | 0.9 µg/mL (IC₅₀) | - [16] |
| **Smenospongidine (35)** | Cytotoxicity | MTT/U251 | 4.0 µM (CC₅₀) | Vehicle-DMSO [26] |
| **5-(+)-Epi-Smenospongidine (36)** | Cytotoxicity | A549 | 3.9 µg/mL (IC₅₀) | - [16] |
| **5-(+)-Epi-Smenospongidine (36)** | Cytotoxicity | HT-29 | 2.4 µg/mL (IC₅₀) | - [16] |
| **Antibacterial** | Broth microdilution/ S. aureus ATCC 25923 | 50.0 µM (MIC) | Moxifloxacin 3.89 µM (MIC) [28] |
| Compound Name         | Biological Activity | Assay, Organism, or Cell Line | Biological Results                  | Ref. |
|-----------------------|---------------------|--------------------------------|-------------------------------------|------|
|                       |                     | Compounds                      | Positive Control                    |      |
|                       |                     |                                |                                     |      |
| Broth microdilution/E. faecalis ATCC 35677 | 50.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
| Isosmenospongine (39) | Cytotoxicity        | MTT/L5178Y                     | 1.69 µM (IC₅₀)                     | [28] |
|                       | Antibacterial       | Broth microdilution/S. aureus ATCC 25923 | 25.0 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 700221 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 35677 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 51299 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 700221 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 35677 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 700699 | 12.5 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 29212 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 29212 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 35677 | 25.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 700221 | 12.5 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
|                       |                     | Broth microdilution/S. aureus ATCC 25923 | 25.0 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
|                       |                     | Broth microdilution/S. aureus ATCC 25923 | 25.0 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
|                       |                     | Broth microdilution/S. aureus USA300 LAC | 2.9 µg/mL (MIC) | Vancomycin 1.0 µg/mL (MIC) | [27] |
|                       |                     | Broth microdilution/S. pyogenes ATCC 12344 | 2.9 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
|                       |                     | Broth microdilution/E. faecium Efm-HS0649 | 1.4 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
|                       |                     | Broth microdilution/S. aureus ATCC 25923 | 50.0 µM (MIC) | Moxifloxacin 3.89 µM (MIC) | [28] |
|                       |                     | Broth microdilution/E. faecalis ATCC 35667 | 50.0 µM (MIC) | Ciprofloxacin 0.02 µM (MIC) | [28] |
|                       |                     | Broth microdilution/S. aureus USA300 LAC | 2.9 µg/mL (MIC) | Vancomycin 1.0 µg/mL (MIC) | [27] |
|                       |                     | Broth microdilution/S. pyogenes ATCC 12344 | 2.9 µg/mL (MIC) | Vancomycin 0.25 µg/mL (MIC) | [27] |
|                       |                     | Broth microdilution/E. faecium Efm-HS0649 | 1.4 µg/mL (MIC) | Vancomycin > 64.0 µg/mL (MIC) | [27] |
|                       | Cytotoxicity        | CCK-8/DU145                     | 24.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/SW1990                    | 21.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Huh7                      | 17.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Panc-1                    | 37.8 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/SW1990                    | 21.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Huh7                      | 17.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Panc-1                    | 37.8 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/DU145                     | 24.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/SW1990                    | 21.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Huh7                      | 17.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Panc-1                    | 37.8 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/DU145                     | 24.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/SW1990                    | 21.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Huh7                      | 17.4 µM (IC₅₀)                     | [32] |
|                       |                     | CCK-8/Panc-1                    | 37.8 µM (IC₅₀)                     | [32] |
Table 3. Cont.

| Compound Name          | Biological Activity | Assay, Organism, or Cell Line                          | Biological Results                                      | Ref.  |
|------------------------|---------------------|--------------------------------------------------------|---------------------------------------------------------|-------|
| (−)-Dictyoceratin C    | Cytotoxicity        | MTT/U251, Panc-1                                        | 4.1 µM (CC<sub>50</sub>)                                 | [26]  |
|                        |                     | MTT/Panc-1                                             | 88.9 µM (CC<sub>50</sub>)                                 |       |
| (−)-Xishaeleganin C    | Antibacterial       | Broth microdilution/S. aureus USA300 LAC               | 11.1 µg/mL (MIC)                                         | [27]  |
|                        |                     | Broth microdilution/S. pyogenes ATCC 12344            | 2.8 µg/mL (MIC)                                          | [27]  |
| (+)-Xishaeleganin D    | Antibacterial       | Broth microdilution/E. faecium Efm-HS0649             | 5.6 µg/mL (MIC)                                          | [27]  |
| (−)-Xishaeleganin B    | Antibacterial       | Broth microdilution/S. aureus USA300 LAC               | 1.5 µg/mL (MIC)                                          | [27]  |
| Pelorol (64)           | Antitrypanosomal    | Semiautomated microdilution/Trichomonas vaginalis     | 17.4 µg/mL (IC<sub>50</sub>)                             | [18]  |
|                        |                     | Antimalarial Semiautomated microdilution/P. falciparum clone | 786.0 µg/mL (IC<sub>50</sub>) | [18]  |
|                        |                     | Semiautomated microdilution/P. falciparum clone NF54 | 1911.0 µg/mL (IC<sub>50</sub>)                           | [18]  |
| Nakijinol B (65)       | Cytotoxicity        | SRB/SF-268                                             | 24.0 µM (GI<sub>50</sub>)                                | [22]  |
|                        |                     | SRB/MCF-7                                              | 35.0 µM (GI<sub>50</sub>)                                | [22]  |
Table 3. Cont.

| Compound Name | Biological Activity | Assay, Organism, or Cell Line | Biological Results | Positive Control | Ref. |
|---------------|---------------------|------------------------------|-------------------|------------------|------|
| SRB/H460      | Cytotoxicity        | CCK-8/DU145                  | 2.87 µM (IC₅₀)    | Cisplatin 2.90 µM (IC₅₀) | [35] |
| SRB/HT-29     | Cytotoxicity        | CCK-8/SW1990                 | 3.55 µM (IC₅₀)    | Cisplatin 5.09 µM (IC₅₀) | [35] |
| SRB/CHO-K1    | Cytotoxicity        | CCK-8/Huh7                   | 3.61 µM (IC₅₀)    | Cisplatin 1.11 µM (IC₅₀) | [35] |
| (-)-Dactyltronic acid A (71) | Antibacterial | Broth microdilution/Vibrio parahemolyticus | 3.45 µM (MIC) | Ciprofloxacin 1.25 µM (MIC) | [33] |
| (-)-Dactyltronic acid B (72) | Antibacterial | Broth microdilution/Vibrio parahemolyticus | 3.45 µM (MIC) | Ciprofloxacin 1.25 µM (MIC) | [33] |
| (+)-Dactylospene B (77) | Anti-inflammatory | Griess reagent/LPS | 77.5% NO inhibition | - | [35] |
| (+)-Dactylospene C (78) | Cytotoxicity | CCK-8/DU145 | 13.35 µM (IC₅₀) | Cisplatin 2.90 µM (IC₅₀) | [35] |
| (-)-Luffariellolide (94) | Cytotoxicity | CCK-8/DU145 | 3.21 µM (IC₅₀) | Cisplatin 2.90 µM (IC₅₀) | [35] |
| (-)-Luffariellolide (94) | Cytotoxicity | CCK-8/SW1990 | 3.55 µM (IC₅₀) | Cisplatin 5.09 µM (IC₅₀) | [35] |
| (-)-Luffariellolide (94) | Cytotoxicity | CCK-8/Huh7 | 3.61 µM (IC₅₀) | Cisplatin 1.11 µM (IC₅₀) | [35] |

- A structure–activity relationship study revealed that 5,6-endocyclic double bond (e.g., mananuthaquione 14), as well as exocyclic double bond (e.g., (−)-ilimaquinone 1 and hyatellaquinone 15) contributed to a high potential towards the BC cell, while the exocyclic double bond (e.g., (−)-ilimaquinone 1) could explain the capacity versus NCI-H187 cell line [21].

- A new sesquiterpene benzoxazole; nakijinol B (65) and two new sesquiterpene quinones; smenospongines B (28) and C (29) along with (−)-ilimaquinone 1 and (−)-dactyloquinone B (5) were purified from methanol extract using RP-18 CC and HPLC. Their structures were elucidated based on spectroscopic analyses (Figure 3). Nakijinol B (65) had a trans-4,9-friedodrimane skeleton linked to benzoxazole moiety, while smenospongines B (28) and C (29) possessed 2-amino-acetic acid and 3-amino-propionic acid moiety at C-20, respectively. Their cytotoxic potential versus a panel of human tumor cell lines; SF-268 (central nervous system-glioblastoma cells), MCF-7 (breast-pleural effusion adenocarcinoma cells), H460 (lung-large cell carcinoma cells), HT-29 (colon-recto-sigmoid colon adenocarcinoma...
Allogeneic BMT (bone marrow transplant) is the only common curative therapy for CML. ATRA (all-trans-retinoic acid) [41]. However, different types of leukemia were found to have a considerable effect versus a panel of 39 solid cancer cell lines was assessed in the SRB and WST-8 (water-soluble tetrazolium salt-8) assays. Smenospongine as an antimicrobial and cytotoxic metabolite from marine organisms. CML is a hematopoietic stem cell cancer produced by the Bcr-Abl kinase [31]. Smenospongine was isolated. Their structures were verified using spectroscopic, ECD (electronic-circular-dichroism), and X-ray analyses (Figure 5). Compounds 46 and 47 possessed an O-bridge among C-17 and C-8 and 5S,8R,9S,10R absolute configuration, as well as isobutylamino and isopentylamino groups, respectively, at C-20; whilst 50 was a hydroquinone sesquiterpene, having 5R,8R,9S,10R configuration based on X-ray and CD analyses.

Their cytotoxic potential was assessed versus SW1990 (human pancreatic cancer), DU145 (human prostate cancer), Huh7 (human liver cancer), and Panc-1 cell lines in the CCK-8 (cell counting kit-8) assay. Compounds 27, 30, 32, and 52 showed activities versus all cell lines (IC50s from 2.33 to 37.85 µM), whereas 45-47 showed no cytotoxicity. It was found that C-8 and C-17 cyclization via O-atom resulted in the loss of inhibitory activity as in 45-47 (IC50 > 50 µM), in comparison to 27, 30, and 32 (IC50 2.33–9.20 µM) [32].

Rodriguez et al. stated that the quinone ring was substantial for the in vitro cytotoxic potential versus the solid tumors, as displayed by the 5-(+)-ilimaquinone (2) and 5-(+)-epi-smenospongiarine (33) potency and dactylospongenones A–D (81–84) inactivity [16].

Differentiation induction therapy is one of the alternative therapeutic methods that is based on the differentiation of tumor cells to normal cells using a differentiation inducer, ATRA (all-trans-retinoic acid) [41]. However, different types of leukemia were found to be unresponsive to ATRA, such as CML (human chronic myelogenous leukemia). So, several exploratory research was carried out to discover new differentiation inducers from marine organisms. CML is a hematopoietic stem cell cancer produced by the Bcr-Abl tyrosine kinase that is resulted from Philadelphia chromosome (Ph) translocation [42]. Allogeneic BMT (bone marrow transplant) is the only common curative therapy for CML. However, the treatment-associated toxicity is dangerous with about 30% reported mortality [43]. Aoki et al. stated that smenosponge (25) (Conc. 3–15 µM) induced K562 CML cells differentiation into erythroblasts alongside with cell cycle arrest at the G1 phase and increased expression of p21 protein, which had an important role in differentiation. Further, it prohibited the phosphorylation of Crkl, which is a substrate of Bcr-Abl tyrosine kinase [31]. Somenosponge 25 an aminooquinone sesquiterpene was firstly reported in 1987 as an antimicrobial and cytotoxic metabolite from S. sp. [44].

Further, in 2008, Kong et al. investigated the influence of 25 on the cell cycles of various cells, including HL60 (human acute promyelocytic leukemia) and U937 (human histiocytic lymphoma) cells, as well as the mechanism of K562 cells G1-phase arrest. It was found to induce dose-dependent apoptosis in U937 and HL60 cells and G1 arrest in K562 cells. In K562 cells, it boosted p21 expression and suppressed Rb phosphorylation, revealing the remarkable function of the p21-Rb pathway in G1 arrest. In addition, it could enhance p21 expression through another mechanism than p21 promoter transactivation [43]. Further, its effect versus a panel of 39 solid cancer cell lines was assessed in the SRB and WST-8 (water-soluble tetrazolium salt-8) assays. Somenosponge 25 suppressed the growth of these cells in vitro (mean Log GI50 -5.55). Additionally, it prohibited migration, proliferation, and
HUVEC (human umbilical vein endothelial cells) tube formation. Hence, it demonstrated antitumor potential versus solid tumors through direct growth inhibition of the tumor cells and anti-angiogenic effectiveness on endothelial cells, indicating its potential as a lead compound for discovering a prominent anticancer [45].

In another study by Aoki et al., a new aminoquinone sesquiterpene, 5- (+)-Epi-Smenospongione (31) and known quinone/hydroquinone sesquiterpenes; 1, 2, 25, 26, 30, 35, 36, 48, and 52 were separated. Compound 31 was presumed to be a hybrid of 30 and 36 and identified a C-5 epimer 30 as confirmed by NOESY (nuclear Overhauser effect spectroscopy). These metabolites were assessed for differentiation-producing potential by induction of hemoglobin production in K562 cells, where the hemoglobin pseudo-peroxidase effect was estimated colorimetrically using diaminofluorene. It was found that 25, 26, 30, 31, 35, and 36 possessed similar K562 cells differentiation-inducing capacity into erythroblasts and were more powerful than aphidicolin; while 48 and 52 had no activity and 2 and 1 had only activity at a higher concentration than those of 25, 26, 30, 31, 35, and 36 [19]. Structure–activity relationship studies revealed that quinone moiety and amino group were crucial for the activity, whereas the substituents at the amino group and C-5 configuration were not essential [20].

A tumor environment’s hypoxic condition is now known as an essential factor for angiogenesis, tumor growth, and metastasis; additionally, at this condition the tumor cells become resistant to irradiation and chemotherapy [23,24]. Thus, the metabolites that selectively prohibit tumor cells growth in the hypoxic environment are expected to be a promising new lead for anticancer agents.

Hypoxia-inducible factor-1 (HIF-1) is a hetero-dimeric transcription factor that comprises an O2-regulated α-subunit and a constitutively expressed β-subunit. Hypoxia induced the HIF-1α subunit O2-dependent hydroxylation, leading to degradation by the proteasome, dimerization of accumulated HIF-1α with HIF-1β, and activation of target genes transcription. HIF-1 activation enhances cancer progression and/or oncogenesis. Furthermore, HIF-1 inhibition causes a decrease in VEGF (vascular endothelial growth factor) expression [24]. As such, HIF-1 has been drawn much interest as a target for chemotherapeutic drugs.

The new metabolites: (−)-5,8-diepi-ilimaquinone (3), (+)-8-epi-dactyloquinone B (6), and 4,5-diepi-dactylospongione (23), along with 1, 21, 22, 24, 61, and 63 were purified from CHCl3 fraction of H2O extract SiO2 and RP-18 CC and characterized by intensive spectroscopic techniques [23]. Compound 3 was a new stereoisomer of 1 and 2, which was identified as a C-8 epimer of 2. On the other side, 23 had C4-C5 cyclopropyl ring instead of the C5-C11 exomethylene in 3 and was assigned as dactylospongione cyclopropyl inverted analog. Additionally, 6, a C-8 epimer of (−)-dactyloquinone B (5) possessed a dihydro-pyran ring that was formed by a C10-O-C17 connection between 4,9-friedodrimane and dialkoxy-1,4-benzoquinone. The activation capacity of these metabolites towards HIF-1 was estimated utilizing colorimetric BCA protein Assay Kits, as well as their cytotoxicity versus MDA-MB-231 and T47D cells in the SRB assay was evaluated [23]. Compounds 1, 3, and 23 with a 2-hydroxy-5-methoxy-1,4-benzoquinone moiety activated HIF-1 at concentrations of 10 and 30 µM. They possessed a high level of HIF induction (930%, 830%, and 1000%, respectively) at 10 µM. However, other compounds had no significant activity, suggesting the 2-hydroxy-1,4-benzoquinone moiety was essential for HIF-1 activation. Further, 1, 3, and 23 (10 µM, 16 h) raised both cellular and secreted VEGF proteins levels in T47D cells similar to 1,10-phenanthroline. VEGF is a HIF-1 target gene that boosts angiogenesis. On the other hand, all metabolites except 63 prohibited T47D cell proliferation more effectively than MDAMB-231 cells, suggesting that the pharmacophores accountable for cell proliferation inhibition and HIF activation were not identical. It was found that the substituted 1,4-benzoquinone’s OH group was substantial for the HIF-1 activating potential (e.g., 1, 3, and 23), whereas its change by ring formation or exchange with a phenol completely abolished the activity [23].
A sesquiterpene phenol, (+)-dictyoceratin C (52) (Conc. 1.0–10 μM) selectively prohibited the DU145 cells proliferation under hypoxic conditions through suppression of HIF-1 accumulation under hypoxic conditions. A structure–activity relationship study was reported utilizing previously reported 1, 12, 25, 26, 30, 31, 36, 38, and 48. (+)-Smenospondiol (48) also demonstrated a similar hypoxia-specific growth inhibition capacity versus DU145 cells as 52, revealing para-hydroxy benzoyl ester moiety was substantial for activity, while the chiral decalin skeleton had no role for activity. On the other side, compounds 1, 12, 25, 26, 30, 31, 36, and 38 containing hydroxyquinone moiety did not demonstrate hypoxia-selective growth inhibition [24].

Additionally, in 2015 Sumii et al. reported the selective prohibition of DU145 proliferation by 49 and 52 under hypoxic conditions and their in vivo antitumor effects in subcutaneously inoculated mice with sarcoma S180 cells with no observed acute toxicities during the study period for these compounds [46]. It was implied that methyl ester, exo-olefinic bond, 8, and OH group were crucial for the hypoxia selective growth inhibition activities of 49 and 52 [45]. Collectively, not only the para-hydroxy-benzoyl moiety but also the decalin skeleton with 8-methyl and 4-exo-cyclic olefinic bond were significant for hypoxia-targeted growth inhibition of 49 and 52 [46,47].

Goclik et al. purified and characterized a new sesquiterpene related to hydroquinones; pelorol (64) and drimane sesquiterpene, 1 from the CH₂Cl₂ soluble fraction using extensive SiO₂ CC and spectroscopic analyses. Compound 64 is a sesquiterpene hydroquinone derivative, having tetracyclic structure with a pentacyclic ring. They had weak anti-trypanosomal and antimalarial potential towards Trypanosoma brucei (IC₅₀ 17.4 and 7.7 μg/mL, respectively) and Plasmodium falciparum clone K1 and clone NF54 (IC₅₀ 786.0 and 1911.0 μg/mL for 64, and 1743.0 and 949.0 for 1, respectively), respectively, in comparison to melarsoprol (IC₅₀ 0.0026 μg/mL for T. brucei) and chloroquine (IC₅₀ 91.0 and 4.6 μg/mL for clone K1 and NF54, respectively) in the semiautomated microdilution method [18]. Additionally, 1 possessed TK (tyrosine kinase) inhibitory effectiveness (87% at Conc. 1.0 μg/mL) [18].

Ebara et al. separated two new drimane sesquiterpenes; dactylospongenones G (85) and dactylospongenone H (86) in addition to, 2, 11, 26, 29, 34, 36, 39–44, and 64 from the n-hexane soluble fraction by SiO₂ CC and HPLC that were unambiguously characterized by NMR spectroscopy and HRESIMS. Dactylospongenones G (85) and dactylospongenone H (86) were isolated as an inseparable mixture, possessing cis 4,9-friedodrim-4(11)-ene and trans-4,9-friedodrim-3(4)-ene skeleton, respectively, with cyclopentadienone moiety. Among these metabolites, 36, 11, 2, 39, 40, and 43 exhibited potent cytotoxic potential (IC₅₀ ranging from 1.3 and 6.48 μM) in comparison to kahalalide F (IC₅₀ 4.30 μM) versus L5178Y (mouse lymphoma) cell line. They were also assessed for antimicrobial capacity versus S. aureus ATCC-25923, S. aureus ATCC-700699, E. faecalis ATCC-29212, E. faecalis ATCC-51299, E. faecalis ATCC-35667, and E. faecalis ATCC-700221 utilizing a broth microdilution method. Pelorol (64) demonstrated moderate to potent antibacterial capacity versus the tested microorganisms (MICs 3.125 to 25 μM) with high effect towards S. aureus (MIC 3.125 μM). None of them had antitubercular capacity versus Mycobacterium tuberculosis [28].

Nakijiquinone V (37), a new aminoquinone sesquiterpenoid, in addition to 1, 25, and 52 were elucidated using NMR and LC-HRESIMS techniques. Nakijiquinone V (37) had Δ⁴,11 friedodrimane quinone skeleton and an imidazole ring connected to the quinone moiety via an amino ethylene group. These metabolites were assessed for antibacterial capacity versus M. luteus ATCC-4698, B. megaterium DSM-32, and E. coli K12. Compounds 1, 25, and 52 had moderate to weak effectiveness versus B. megaterium DSM32 (MICs 32, 32, and 64 μg/mL, respectively). Further, 1 and 25 (MIC of 32 μg/mL) prohibited M. luteus ATCC-4698 [25].

New sesquiterpene hydroquinones; (-)-xishaeleganin A (56), B (57), C (54), and D (55), along with known related metabolites 1, 2, 4, 5, 7–9, 49, 51, 52, and 53 were separated from E₂O fraction of acetone extract using SiO₂, Sephadex LH-20, and RP-HPLC. Compound 56, hydroquinone sesquiterpene with farnesyl moiety was related to 4-hydroxy-3-methoxy-5-(2E,6E)-7,11-trimethyldeca-2,6,10-trien-1-yl)benzoic acid reported from
Aspergillus flavipes [48]. Additionally, 57 is a drimane sesquiterpene similar to ent-yahazunol reported from Dysidea genus sponge [49], however, it showed 1,2,3,5-tetrasubstituted hydroquinone, instead of a 1,2,4-tri-substituted hydroquinone. Compounds 54 and 55 are 4,9-friedodrimane sesquiterpene hydroquinones in which the sesquiterpene skeleton connected to hydroquinone through C1–C17 ether linkage and direct C10–C17 carbon linkage, respectively, to produce a seven-membered ring (in 54) and five-membered ring (in 55). These metabolites were tested for antibacterial potential versus S. aureus USA300-LAC, S. pyogenes ATCC-12344, and E. faecium Efm-HS0649 in the broth microdilution method. Compounds 1, 2, 49, and 57 had marked antibacterial capacity versus S. aureus (MICs 5.6, 5.6, 2.9, and 1.5 \( \mu \text{g/mL} \)) in comparison to vancomycin (MIC 1.0 \( \mu \text{g/mL} \)). As for S. pyogenes, compounds 1, 2, 7, 49, 51, 54, and 57 demonstrated significant antibacterial effectiveness (MICs ranged from 1.5 to 5.6 \( \mu \text{g/mL} \)). In addition, compounds 7, 49, 51, 54, and 57 displayed significant potential versus E. faecium (MICs 1.4–5.6 \( \mu \text{g/mL} \)). These results suggested that the sesquiterpene quinones/hydroquinones as 57 and 49 possessed the possibility to be the new lead metabolites of antibiotics [27].

2.1.2. Sesquiterpene Quinone/Hydroquinone Dimers

Li et al. reported the characterization of popolohuanones B (66), C (67), G (68), H (69), and I (70) that are dimeric sesquiterpenes, having linked quinone and hydroquinone moieties through either amine or ether bridge (C19-O-C20' as in 66, C19-N-C20' as in 67, or C18-N-C20' as in 68, 69, and 70). In the CCK-8 cytotoxicity assay, these metabolites had no cytotoxic potential versus HT-29, PC-9, A375, HepG2, and MCF-7. On the other hand, only 69 displayed potent IL-6 production inhibitory influence that was induced by LPS in the THP-1 cells with (%inhibition 73.1%, Conc. 10 \( \mu \text{g/mL} \)). It was assumed that the C19–NH–C20' amine bridge among the hydroquinone and quinone moiety could be the active moiety for popolohuanones [34] (Figure 6).

2.1.3. Sesquiterpene Tetronic Acids

Sesquiterpene tetronic acids are a rare class of sesquiterpenes with 4-hydroxy-[5H] furan-2-one moiety linked to the sesquiterpene skeleton. (−)-Dactyltronic acids (A/B 71/72) were separated as a mixture of inseparable isomers from the EtOAc by SiO\textsubscript{2} and Sephadex CC, as well as HPLC. Dactyltronic acids A/B (71/72) had pronounced antibacterial potential towards V. parahemolyticus (MIC 3.45 \( \mu \text{M} \)) relative to ciprofloxacin (MIC 1.25 \( \mu \text{M} \)), whereas compounds 52 and 53 were weakly active [33] (Figure 7).

2.2. Seseterpenes

Chemical investigation of D. elegans afforded new \( \gamma \)-oxygenated utanolide seseterpene derivatives; dactylospenes A (95) and B-E (77–80), in addition to structurally related compounds; furospinoolins B (93) and (−)-luffariellolide (94) that were characterized based on spectroscopic and ECD analyses. Only compounds 78, 94, and 95 (IC\textsubscript{50} 2.11–13.35 \( \mu \text{M} \)) possessed moderate cytotoxic potential versus Huh7, DU145, SW1990, and PANC-1 in the CCK-8 assay. These results indicated that R-\( \gamma \)-methoxy utanolide unit influenced positively the activity [35].

Arai et al. found that the furanosesterterpene; furospinoolin-1 (92) (Conc. 1–100 \( \mu \text{M} \)) demonstrated an in vitro selective antiproliferative potential versus DU145 (human prostate cancer cells) under hypoxic conditions [50]. Additionally, it had antitumor potential without adverse influences upon administration (Conc. 10–50 \( \mu \text{g/kg, orally} \)) in a sarcoma S180-inoculated mouse model. Further mechanistic studies indicated that 92 repressed IGF-2 (insulin-like growth factor-2) gene transcription that is selectively produced under hypoxia through the prohibition of the nuclear proteins binding to the Sp1 consensus sequence in the IGF-2 promoter region, while it did not prohibit HIF-1\( \alpha \) production (hypoxia-inducible factor-1\( \alpha \)) [49,50]. It could also prohibit IGF-IR signaling (insulin growth factor 1 receptor) through IGF-2 transcription suppression [51]. Accordingly, furospinoolin-1 may be a potential lead for anticancer agents, which target hypoxia-acclimatized cancer cells [49].
Furospinosulin-1 (92) also had inhibitory potential versus HCT-116 (human colon cancer, IC$_{50}$ 155 µM) and Cdc25A (IC$_{50}$ 2.5 µM) [52,53].

2.3. Diterpenes

Dolabellane diterpenes are diterpenoids with a dolabellane skeleton, consisting of an unusual trans-bicyclo[9.3.0]tetradecane nucleus. A rare diterpene, (+)-eleganstone A (88), having a 5/6/4/5-fused tetracyclic skeleton and a new dolabellane diterpene; (+)-(1R*, 2E,4R*,8E,10S*,11S*,12R*)-10,18-diacetoxydolabella-2,8-dien-6-one (90), and formerly reported 89 and 91 were separated from CH$_2$Cl$_2$ fraction using RP-18 and HPLC and elucidated by spectroscopic and ECD analyses. Compounds 89 and 91 are a pair of Z/E isomers that were interconverted by light-induced isomerization. These metabolites had no cytotoxic effectiveness (IC$_{50}$ > 50 µM) versus HCT-116, 22RV1 (human prostate carcinoma epithelial cell line), MCF-7 (human breast cancer), and K562 (human chronic leukemia) in the CCK-8 assay. On the other hand, only 89 demonstrated potent antibacterial capacities towards E. coli, B. subtilis, and S. aureus (MIC 32 µg/mL) in the broth dilution method [36].

2.4. Sterols and Pregnanes

Pregna-1,20-dien-3-one (96) and 3-hydroxycholesta-5,8-dien-7-one (97) were purified from the EtOAc fraction. Compound 96 displayed antibacterial potential (MIC 4.19 µM) versus B. cereus, comparing to ciprofloxacin (MIC 1.25 µM), while 97 had a weak activity [33] (Figure 9). The cytotoxicity assessment using CCK-4 assay of steroid derivatives; 98–100 versus HepG 2, HT-29, and MCF-7 revealed that 98 and 99 displayed notable cytotoxic capacities versus MCF-7 (IC$_{50}$ 9.7 and 8.5 µM, respectively). However, they had weak to no activity towards the other cell lines [37].

2.5. Other Metabolites

Neupane et al. separated kauamide (101), a new chlorinated metabolite with a rare 11-membered heterocyclic skeleton. The structure of 101 was verified by spectroscopic analyses and its 3S, 6S, 11S, and L-leucine stereoconfigurations were established from GIAO (gauge-independent atomic orbital) NMR shielding tensors DFT (density functional theory) calculations, and Marfey’s analysis. It had no BACE1 inhibitory potential and cytotoxic activity against U251 and Panc-1 cell lines in the MTT assay [26].

Figure 1. Structures of compounds 1–12.
Figure 2. Structures of compounds 13–24.

Figure 3. Structures of compounds 25–36.
and 49 having the most potent influences (CC50s 2.4 and 2.8 µM, respectively) [26]. Further, 27, 30, 32, 45, and 51 were significantly active versus Panc-1 (human pancreatic cancer) cells (CC50s ranged from 12.6 to 22.6 µM) [26].

**Figure 4.** Structures of compounds 37–48.

Using SiO2, RP-18, and HPLC, three new sesquiterpenes; 46, 47, and 50, along with 27, 30, 32, 45, and 52 were isolated. Their structures were verified using spectroscopic, ECD (electronic-circular-dichroism), and X-ray analyses (Figure 5). Compounds 46 and 47 possessed an O-bridge among C-17 and C-8 and 5S,8R,9S,10R absolute configuration, as well as isobutylamino and isopentylamino groups, respectively, at C-20; whilst 50 was a hydroquinone sesquiterpene, having 5R,8R,9S,10R configuration based on X-ray and CD analyses.

**Figure 5.** Structures of compounds 49–60.

Their cytotoxic potential was assessed versus SW1990 (human pancreatic cancer), DU145 (human prostate cancer), Huh7 (human liver cancer), and Panc-1 cell lines in the CCK-8 (cell counting kit-8) assay. Compounds 27, 30, 32, and 50 showed activities versus all cell lines (IC50s from 2.33 to 37.85 µM), whereas 45–47 showed no cytotoxicity. It was found that C-8 and C-17 cyclization via O-atom resulted in the loss of inhibitory activity as in 45–47 (IC50 > 50 µM), in comparison to 27, 30, and 32 (IC50 2.33–9.20 µM) [32].

Rodriguez et al. stated that the quinone ring was substantial for the in vitro cytotoxic potential versus the solid tumors, as displayed by the 5-(+)-epi-ilimaquinone (2) and 5-(+)-epi-smenospongiarine (33) potency and dactylospongenones A–D (81–84) inactivity [16].

Differentiation induction therapy is one of the alternative therapeutic methods that is based on the differentiation of tumor cells to normal cells using a differentiation inducer, ATRA [41]. However, different types of leukemia were found to be unresponsive to ATRA, such as CML (human chronic myelogenous leukemia). So, several exploratory research was carried out to discover new differentiation inducers from marine organisms. CML is a hematopoietic stem cell cancer produced by the Bcr-Abl tyrosine kinase that is resulted from Philadelphia chromosome (Ph) translocation.
2.1.3. Sesquiterpene Tetronic Acids

Sesquiterpene tetronic acids are a rare class of sesquiterpenes with 4-hydroxy-[5H]-furan-2-one moiety linked to the sesquiterpene skeleton. (+)-Dactyltronic acids (A/B 71/72) were separated as a mixture of inseparable isomers from the EtOAc by SiO2 and Sephadex CC, as well as HPLC. Dactyltronic acids A/B (71/72) had pronounced antibacterial potential towards *V. parahemolyticus* (MIC 3.45 µM) relative to ciprofloxacin (MIC 1.25 µM), whereas compounds 52 and 53 were weakly active [33] (Figure 7).

2.2. Sesterterpenes

Chemical investigation of *D. elegans* afforded new γ-oxygenated utanolide sesterterpene derivatives; dactylospenes A (95) and B-E (77–80), in addition to structurally related compounds; furospinosulin B (93) and (-)-luffariellolide (94) that were characterized based on spectroscopic and EC D analyses. Only compounds 78, 94, and 95 (IC50s 2.11–13.35 µM) possessed moderate cytotoxic potential versus Huh7, DU145, SW1990, and PANC-1 in the CCK-8 assay. These results indicated that R-γ-methoxy utanolide unit influenced positively the activity [35].

Figure 6. Structures of compounds 61–70.

Figure 7. Structures of compounds 71–80.
Arai et al. found that the furanosesterterpene, furospinosulin-1 \((92)\) (Conc. 1–100 µM) demonstrated an in vitro selective antiproliferative potential versus DU145 (human prostate cancer cells) under hypoxic conditions [50]. Additionally, it had antitumor potential without adverse influences upon administration (Conc. 10–50 mg/kg, orally) in a sarcoma S180-inoculated mouse model. Further mechanistic studies indicated that \(92\) repressed \(IGF-2\) (insulin-like growth factor-2) gene transcription that is selectively produced under hypoxia through the prohibition of the nuclear proteins binding to the Sp1 consensus sequence in the \(IGF-2\) promoter region, while it did not prohibit HIF-1\(\alpha\) production (hypoxia-inducible factor-1\(\alpha\)) [49,50]. It could also prohibit IGF-IR signaling (insulin growth factor 1 receptor) through IGF-2 transcript ion suppression [51]. Accordingly, furospinosulin-1 may be a potential lead for anticancer agents, which target hypoxia-acclimatized cancer cells [49]. Furospinosulin-1 \((92)\) also had inhibitory potential versus HCT-116 (human colon cancer, IC50 155 µM) and Cdc25A (IC50 2.5 µM) [52,53].

2.3. Diterpenes

Dolabellane diterpenes are diterpenoids with a dolabellane skeleton, consisting of an unusual \(\text{trans}\)-\(\text{bicyclo [9.3.0]tetradecane}\) nucleus. A rare diterpene, \((+)-\text{eleganstone A} (88)\), having a \(5/6/4/5\)-fused tetracyclic skeleton and a new dolabellane diterpene; \((+)-\text{eleganstone B} (89)\), were reported with anti-tumor activity [56].

3. Biosynthetic Pathways of \(D.\) elegans Metabolites

Several studies reported the biosynthetic pathways of the reported sesquiterpenes from this sponge. In this work, the reported postulated pathways were summarized. It was reported that the observed differences in stereochemistry among the marine sesquiterpene metabolites could be inferred from the precursor binding preferences within a single cyclase enzyme active site [54]. Additionally, this may be due to the existence of various synthase enzymes, whereas each individual enzyme can create a range of diverse metabolites, as well as presumably the potential to change the stereochemical outcomes, depending on the provided substrate nature. Thus, the possibility of enantiomeric metabolites should be considered that emphasizes the significance of reporting \([\alpha]D\) values for these terpenes in cases where they are utilized as a reference in the stereochemical determination [21,55].

Boufridi et al. hypothesized that the biosynthetic process of \(1\) and \(2\) started with the farnesylation of the aromatic ring, which is the quinone moiety’s precursor to obtain \(\text{I}\). This involves the initial folding of \(\text{I}\) within the active site of a specific terpene cyclase (Scheme 1). Successively, two carbocationic intermediates \(\text{II}\) and \(\text{III}\) are resulted from peri-planar Wagner–Meerwein hydrogen and methyl shifts. Finally, \(\text{III}\) may undergo two pathways (A or B) for the formation of \(1\) and \(2\) through the loss of a proton from carbocations \(\text{IV}\) and \(\text{V}\), respectively [40].
3. Biosynthetic Pathways of D. elegans Metabolites

Several studies reported the biosynthetic pathways of the reported sesquiterpenes from this sponge. In this work, the reported postulated pathways were summarized. It was reported that the observed differences in stereochemistry among the marine sesquiterpene metabolites could be inferred from the precursor binding preferences within a single cyclase enzyme active site [54]. Additionally, this may be due to the existence of various synthase enzymes, whereas each individual enzyme can create a range of diverse metabolites, as well as presumably the potential to change the stereochemical outcomes, relying on the provided substrate nature. Thus, the possibility of enantiomeric metabolites should be considered that emphasize the significance of reporting $[\alpha]_D$ values for these terpenes in cases where they are utilized as a reference in the stereochemical determination [21,55].

Boufridi et al. hypothesized that the biosynthetic process of 1 and 2 started with the farnesylation of the aromatic ring, which is the quinone moiety’s precursor to obtain I. This involves the initial folding of I within the active site of a specific terpene cyclase (Scheme 1). Successively, two carbocationic intermediates II and III are resulted from peri-planar Wagner–Meerwein hydrogen and methyl shifts. Finally, III may undergo two pathways (A or B) for the formation of 1 and 2 through the loss of a proton from carbocations IV and V, respectively [40].

Yong et al. postulated that 13, 15, 16, 19, 20, and 22 may be originated from the cationic intermediate (I) (Scheme 2). The introduction of double bond yields 16. The cyclization of 16 (pathway A), or hydride migration with subsequent cyclization forming 22 and its related cyclic intermediate ent-cyclospongiaquinone-2 (II), then the formation of double bond yields 19 and 20 (pathway B). Finally, the hydride migration and loss of a proton from the cationic site adjacent methyl form 13 with a cyclopropyl ring (pathway C) [21].

![Scheme 1](image_url)
Scheme 2. Postulated biosynthetic pathways for 13, 15, 16, 19, 20, and 22 [21].

Scheme 3 shows that the farnesyl precursor (I) initial cyclization gives II (enantiomeric cation) that undergoes a loss of a proton to give 16 and 21. On the other side, cation II’s hydride and methyl migrations yield compounds 1, 14, and 18 [21].

Scheme 3. Postulated biosynthetic pathways for 1, 14, 16, 18, and 21 [21].
Diacetoxydolabella-2,7-dien-6-one (89) was proposed to be the biogenetic precursor of 88. (+)-Elegantone A (88) may be originated from diacetoxydolabella-2,7-dien-6-one (89) through intramolecular [2 + 2] cycloaddition. The coupling of Δ^{7,8} and Δ^{2,3} in 89 via the endo-cycloaddition generates 88 (Scheme 4) [36,56].

![Scheme 4](image_url)

**Scheme 4.** Proposed biosynthetic pathway for 88 [36].

### 4. Synthesis of *D. elegans* Metabolites

Some of the reported metabolites from this sponge possessed fascinating bioactivities, such as anticancer. Nevertheless, further biological investigation is limited due to the not enough isolated metabolites. Therefore, research interests have been directed towards synthesis and structural modification of these metabolites to improve the bioactivities and study structural/activity relations, which could help in drug development and discovery. Some of these studies have been highlighted here.

Kotoku et al. synthesized several analogs of furospinosulin-1 (92) and assessed their selective hypoxia inhibitory potential (Scheme 5) [57].

![Scheme 5](image_url)

**Scheme 5.** Synthesis of furospinosulin-1 (92) analogues [57].

It was found that only the analog (FA) with desmethyl near to the furan ring had an excellent hypoxia-specific growth inhibitory potential such as furospinosulin-1 (92) and displayed greater in vivo antitumor potential in oral administration (doses 1–10 μM) versus DU145 cells, as well as lower toxicity in normal conditions (dose 300 µM) [57]. Therefore, this analog might be better than furospinosulin-1 for drug candidates.

Kotoku et al. reported that the modifications of 92 structure such as elongating the methyl group close to the furan ring, changing the aromatic ring, and side-chain truncation...
led to a remarkable loss of selective hypoxia growth inhibition capacity, obviously revealing that the entire structure was substantial for the binding with the target molecule [58], whilst the analog had a longer side chain partially retained hypoxia-selective inhibitory potential. Therefore, Kotoku et al. synthesized and assessed various furospinosulin-1 (92) tail-modified analogs (Scheme 6).  

\[ \text{Scheme 6. Synthesis of tail-modified analogues of furospinosulin-1 (92) [58].} \]

The analog X was found to be much more potent than furospinosulin-1 as it possessed hypoxia-selective growth-inhibitory potential (Conc. 1–300 µM) and had powerful in vivo antitumor effectiveness after oral administration (doses 5–25 mg/kg) without side effects [58].

Additionally, in 2015, Sumii et al. assessed the structure–activity relationship of (+)-dictyoceratin A (49) and (+)-dictyoceratin C (52) through the synthesis of structural-modified derivatives of (+)-dictyoceratin C (52) and testing their in vivo antitumor potential [47]. Thus far, the only methyl ester substitution in 52 with propargyl amide (DA) had an excellent hypoxia-selective growth prohibition potential at 30 µM relative to 52 (Scheme 7). Thus, it could be efficient for probe molecules synthesis for target identification of 49 and 52 [47].
Pelorol (64), sesquiterpene hydroquinone having C8–C21 cyclization had a potent and selective SHIP1 (Src homology 2-containing inositol 5-phosphatase 1) activating potential [59]. However, this compound had catechol moiety that can be either enzymatic or chemically oxidized to orthoquinones, forming covalent linkages with proteins resulting in losing the activity. Additionally, it is highly water-insoluble, which limits its in vivo bioactivity as a SHIP1 activator. Meimetis et al. synthesized more water-soluble amino analogs ent-PA or (±)-PA (Scheme 8). Synthesis of (±)-PA characterized by generating a tetracyclic ring system through a cation-initiated polyene cyclization [60]. Then, 3,5-Dimethoxybromobenzene lithiation subsequent alkylation with farnesyl bromide produced the 3,5-dimethoxybenzene prenylated intermediate. A racemic epoxide was produced utilizing the 3,5-dimethoxybenzene prenylated intermediate. 3-Hydroxy-2-(3H-indolin-1-yl)-2-methyl-5-nitrobenzofuran (±)-Shi catalyst produced (±)-PA (Scheme 8). Synthesis of (±)-PA characterized by generating (±)-PA. Repeating the same procedure using ent-Shi catalyst produced ent-PA analog. These analogs in vitro activated SHIP1, prohibited Akt phosphorylation and had potent in vivo anti-inflammation potential (ED50 0.1 mg/kg, oral gavage) using passive cutaneous anaphylaxis mouse model [60]. The results suggested that ent-PA or (±)-PA pelorol analogs are promising candidates for further in vivo preclinical investigation as SHIP1-activating therapeutics for treating hematopoietic illnesses, involving aberrant PI3K cell signaling activation.

Scheme 7. Synthesis of potent structurally modified analog of 52 [47].

Scheme 8. Synthesis of SHIP1-activating analogs of pelorol (64) [60].
5. Activities of *D. elegans* Extracts and Fractions

BACE1 (β-site of amyloid precursor protein cleaving enzyme) is an enzyme involved in Alzheimer’s disease pathogenesis. The 75% and 100% MeOH C8 fractions of *D. elegans* obtained from the coast of Kauai had significant in vitro BACE1 inhibition (% inhibition 66% and 73%, respectively, at Conc. 30 µg/mL) [61]. Li et al. revealed that the CH$_2$Cl$_2$/MeOH extract possessed marked IL-6 and TNF-α inhibitory potential [34]. Additionally, the antioxidant potential testing revealed that *D. elegans* hexane extract exhibited significant antioxidant potential in comparison to the ascorbic acid [62].

6. Conclusions

The marine environment is a wealth of biological and chemical diversity. Biometabolites from marine organisms have been proven to be beneficial sources for the discovery of novel drug targets. Among these organisms, sponges are a fascinating marine invertebrate' phylum, which have been recognized as a big reservoir of biometabolites. The current work highlights one of the most interesting sponge species, *D. elegans*. Over the last 30 years, 101 metabolites have been separated and characterized from *D. elegans*. The results displayed that sesquiterpenes of various classes represented the major metabolites of this sponge. Additionally, few studies reported the isolation of sesterterpenes, sterols, pregnanes, and diterpenes (Figure 10).

![Figure 10. Number and chemical class of reported metabolites from *D. elegans*.](image)

These metabolites have been assessed mainly for their antitumor and antiproliferative potential. Limited studies investigated the antibacterial, anti-inflammatory, β-secretase 1 inhibitory, and antiprotozoal activities (Figure 11).

Some *D. elegans* sesquiterpenes demonstrated remarkable cytotoxic and antiproliferative activities either in vivo or in vitro towards various cancer cell lines. Further, some sesquiterpenes had promising HIF-1 activating capacity, therefore they could have therapeutic potential as future drug targets for chemotherapeutic drugs, as well as for treating ischemic diseases.

It is noteworthy that limited studies exploring the mechanism of anticancer potential of these metabolites were reported. It was found that these metabolites induced their effectiveness through any of the following mechanisms: hypoxia-targeted growth inhibition (e.g., 48, 49, and 52), inhibition of IGF-IR signaling via IGF-2 transcription suppression.
(e.g., 92), inhibiting accumulation of HIF-1 and decreasing production of VEGF (e.g., 52), induction of apoptosis through increasing proteolytic activity of caspases (e.g., 1 and 2), and cell cycle arrest through boosting p21 expression and suppressing Rb phosphorylation (e.g., 25). Further, one report revealed the anti-inflammatory potential of 69 through inhibition of IL-6 production.

**Figure 11.** Bioactivities and the number of tested metabolites.

The structure–activity studies demonstrated that the chemical nature of the metabolites’ skeletons, as well as the substituents, were greatly influenced the activities as summarized in Figures 12 and 13.

**Figure 12.** Structural features of sesquiterpene phenols and structure–activity relationship (SAR) hypoxia-selective growth inhibition. Decalin part: blue-colored; P-Hydroxybenzoyl: red-colored; exo-olefin: pink-highlighted; Methyl ester: orange-highlighted; 8-Methyl: green-highlighted [24,46,47].
we believed that the metabolites of this sponge deserve much more research attention. Advanced techniques, such as metabolomics, LC/MS/NMR (liquid chromatography/mass spectrometry/nuclear magnetic resonance), and UPLC/MS (Ultra performance liquid chromatography-tandem mass spectrometer) should be employed to explore more biologically active and useful tags for further functionalization of these metabolites through click chemistry which is a new field for synthesizing drug-like molecules that can accelerate the process of drug discovery. Interestingly, kauamide was proposed to be biosynthesized by cyanobacteria harboring *D. elegans* due to its structure similarity to cyanobacteria reported metabolites, therefore the chemical investigation of symbiotic microorganisms of *D. elegans* could be potential producers of biometabolites originally derived from this sponge.

Moreover, some bioassays of the reported metabolites revealed no potential effectiveness, providing more potentiality for carrying out other pharmacologic evaluations. Advanced techniques, such as metabolomics, LC/MS/NMR (liquid chromatography/mass spectrometry/nuclear magnetic resonance), and UPLC/MS (Ultra performance liquid chromatography-tandem mass spectrometer) should be employed to explore more biometabolites from this sponge. A combination of pathway reconstructing, genetic and enzyme engineering, and metabolic networks could modify this sponge to biosynthesize more novel metabolites having promised structural features or a large quantity of the valuable known ones for pharmaceutical application. Structure–activity relationship studies and chemical syntheses of the promising metabolites give further chances to generate more significant drug leads with optimized chemical stability, activity, and accessibility. Finally, we believed that the metabolites of this sponge deserve much more research attention.

**Author Contributions:** Conceptualization, S.R.M.I., H.M.A. and G.A.M.; resources, S.A.F., H.A.F., R.H.H. and S.O.A.; data curation, S.A.F., H.A.F., R.H.H. and S.O.A.; writing—original draft preparation, S.R.M.I., H.M.A. and G.A.M.; writing—review and editing, S.A.F., H.A.F., R.H.H., S.O.A., S.R.M.I. and G.A.M. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.
Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

A549: Lung adenocarcinoma epithelial cell line; A375: Human melanoma cell line; L5178Y: Mouse lymphoma cell line; ATRA: all-trans-retinoic acid; B16F10: Human murine melanoma cell; BACE1: Fluorescent beta secretase assay kits; BC: Human breast cancer cell line; CCK-8: Cell Counting Kit-8; BCR-ABL: Mutation that is formed by the combination of two genes; BMT: Bone marrow transplant; C50: Cytotoxicity concentration 50; CH2Cl2: Dichloromethane; CIP/KIP: Family cyclin-dependent kinase; CML: Chronic myelogenous leukemia; Crkl: Adaptor protein; DU145: Human prostate cancer cell line; ECD: Electronic circular dichroism; Et2O: Diethyl ether; EtOAc: Ethyl acetate; EtOH: Ethanol; GI50: Growth inhibitory power of the test agent; H2O: Water; HIF-1: Hypoxia-inducible factor-1; HL60: Human acute promyelocytic leukemia cell line; HT-29: Human colon adenocarcinoma cell line; Huh7: Human liver cancer cell lines; HepG2: Human hepatocarcinoma cell line; HPLC: High pressure liquid chromatography; HUVEC: Human umbilical ven endothelial cells; IGF-2: Insulin-like growth factor-2 gene; IC50: Concentration causing 50% growth inhibition; LEDGF/p75: Lens epithelium-derived growth factor p75; LPS: Lipopolysaccharide; K562: Human chronic myelogenous leukemia cell line; LC/MS/NMR: Liquid chromatography/mass spectrometry/nuclear magnetic resonance; MCF-7: Human breast cancer cell line; MDA-MB-231: Epithelial, human breast cancer cell line; MeOH: Methanol; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NCI-H187: Human small cell lung cancer cell line; NMR: Nuclear magnetic resonance; NOESY: Nuclear Overhauser Effect Spectroscopy; NO: Nitrous oxide; RP-18: Reversed-phase C18 silica gel; Panc-1: Human pancreatic carcinoma cell lines; P3: Human epithelial teratocarcinoma cells; P21: Potent cyclin-dependent kinase inhibitor; P388: Leukemia cell line; PC-3: Human prostate cancer cell line; PC-9: Human adenocarcinoma cell line; p54nrb: Non-POU domain-containing octamer-binding protein; Ph: Philadelphia chromosome; SRB: Sulfurhodamine B; SiO2: Silica gel column chromatography; Sp1: Proximal specificity protein 1; SW1990: Human pancreatic cancer cell line; T-47D: Human breast cancer cell line; THP-1: Human acute monocytic leukemia cell line; U251: Human glioma cell lines; U937: Human histiocytic lymphoma cell line; UPLC/MS: Ultra performance liquid chromatography-tandem mass spectrometer; VEGF: Vascular endothelial growth factor; WST-8: Colorimetric Cell Viability Kit; WST-8: Water-soluble tetrazolium salt-8.

References

1. Kobayashi, J. Search for new bioactive marine natural products and application to drug development. Chem. Pharm. Bull. 2016, 64, 1079–1083. [CrossRef]
2. Omar, A.M.; Mohamed, G.A.; Ibrahim, S. Chaetomugilins and chaetoviridins-promising natural metabolites: Structures, separation, characterization, biosynthesis, bioactivities, molecular docking, and molecular dynamics. J. Fungi 2022, 8, 127. [CrossRef] [PubMed]
3. Radjasa, O.K.; Vaske, Y.M.; Navarro, G.; Vervoort, H.C.; Tenney, K.; Linington, R.G.; Crews, P. Highlights of marine invertebrate-derived biosynthetic products: Their biomedical potential and possible production by microbial associants. Bioorg. Med. Chem. 2011, 19, 6658–6674. [CrossRef]
4. Gerwick, W.H.; Moore, B.S. Lessons from the past and charting the future of marine natural products drug discovery and chemical biology. Chem. Biol. 2012, 19, 85–98. [CrossRef] [PubMed]
5. Mohamed, G.A.; Ibrahim, S.R.M. Untapped potential of marine-associated Cladosporium species: An overview on secondary metabolites, biotechnological relevance, and biological activities. Mar. Drugs 2021, 19, 645. [CrossRef] [PubMed]
6. Gao, Z.M.; Zhou, G.W.; Huang, H.; Wang, Y. The Cyanobacteria-dominated sponge Dactylospongia elegans in the South China Sea: Prokaryotic community and metagenomic insights. Front. Microbiol. 2017, 8, 1387. [CrossRef] [PubMed]
7. Hentschel, U.; Hopke, J.; Horn, M.; Friedrich, A.B.; Wagner, M.; Hacker, J.; Moore, B.S. Molecular evidence for a uniform microbial community in sponges from different oceans. Appl. Environ. Microbiol. 2002, 68, 4431–4440. [CrossRef] [PubMed]
8. Esposito, R.; Ruocco, N.; Viel, T.; Federico, S.; Zupo, V.; Costantini, M. Sponges and their symbionts as a source of valuable compounds in cosmeceutical field. Mar. Drugs 2021, 19, 444. [CrossRef] [PubMed]
9. Bell, J.I. The functional roles of marine sponges. Estuar. Coast. Shelf Sci. 2008, 79, 341–353. [CrossRef]
10. Lee, Y.K.; Lee, J.H.; Lee, H.K. Microbial symbiosis in marine sponges. J. Microbiol. 2001, 39, 254–264.
11. Thomas, T.R.; Kavlekar, D.P.; LokaBharathi, P.A. Marine drugs from sponge-microbe association-a review. Mar. Drugs 2010, 8, 1417–1468. [CrossRef] [PubMed]
12. Galitz, A.; Nakao, Y.; Schupp, P.J.; Wörheide, G.; Erpenbeck, D. A soft spot for chemistry–current taxonomic and evolutionary implications of sponge secondary metabolite distribution. *Mar. Drugs* **2021**, *19*, 448. [CrossRef] [PubMed]

13. Sladić, D.; Gasić, M.J. Reactivity and biological activity of the marine sesquiterpene hydroquinone avarol and related compounds from sponges of the order Dictyoceratida. *Molecules* **2006**, *11*, 1–33. [CrossRef] [PubMed]

14. Sagar, S.; Kaur, M.; Minneman, K.P. Antiviral lead compounds from marine sponges. *Mar. Drugs* **2010**, *8*, 2619–2638. [CrossRef] [PubMed]

15. Wada, Y.; Fujihara, K.; Kita, Y. Synthesis of the marine pyrroloiminoquinone alkaloids, discorhabdins. *Mar. Drugs* **2010**, *8*, 1394–1416. [CrossRef] [PubMed]

16. Rodríguez, J.; Quiñoñó, E.; Riguera, R.; Peters, B.M.; Abrell, L.M.; Crews, P. The structures and stereochemistry of cytotoxic sesquiterpene quinones from *Dactylospongia elegans*. *Tetrahedron* **1992**, *48*, 6667–6680. [CrossRef]

17. López, M.D.; Quiñoñó, E.; Riguera, R. Dactyltronic acids from the sponge *Dactylospongia elegans*. *J. Nat. Prod.* **1994**, *57*, 992–996. [CrossRef] [PubMed]

18. Goclick, E.; König, G.M.; Wright, A.D.; Kaminsky, R. Pelorol from the tropical marine sponge *Dactylospongia elegans*. *J. Nat. Prod.* **2000**, *63*, 1150–1152. [CrossRef]

19. Mitome, H.; Nagasawa, T.; Miyaoka, H.; Yamada, Y.; van Soest, R.W. Dactyloquinones A and B, new sesquiterpenoid quinones from the Okinawan marine sponge, *Dactylospongia elegans*. *Tetrahedron* **2002**, *58*, 1693–1696. [CrossRef]

20. Aoki, S.; Kong, D.; Matsu, K.; Rachmat, R.; Kobayashi, M. Sesquiterpene aminoquinones from a marine sponge, induce erythroid differentiation in human chronic myelogenous leukemia, K562 cells. *Chem. Pharm. Bull.* **2004**, *52*, 935–937. [CrossRef]

21. Yong, K.W.L.; Jankam, A.; Hooper, J.N.A.; Suksamrarn, A.; Garson, M.J. Stereochemical evaluation of sesquiterpene quinones from two sponges of the genus *Dactylospongia* and the implication for enantioselective processes in marine terpene biosynthesis. *Tetrahedron* **2008**, *64*, 6341–6348. [CrossRef]

22. Ovenden, S.P.; Nielson, J.L.; Liptrot, C.H.; Willis, R.H.; Tapiolas, D.M.; Wright, A.D.; Motti, C.A. Sesquiterpene benzoxazoles and sesquiterpene quinones from the marine sponge *Dactylospongia elegans*. *J. Nat. Prod.* **2011**, *74*, 65–68. [CrossRef] [PubMed]

23. Du, L.; Zhou, Y.D.; Nagle, D.G. Inducers of hypoxic response: Marine sesquiterpene quinones activate HIF-1. *J. Nat. Prod.* **2013**, *76*, 1175–1181. [CrossRef]

24. Arai, M.; Kawachi, T.; Sato, H.; Setiawan, A.; Kobayashi, M. Marine spongian sesquiterpene phenols, dictyoceratin-C and smenospondiol, display hypoxia-selective growth inhibition against cancer cells. *Biomedicines* **2017**, *5*, 63. [CrossRef] [PubMed]

25. Balansa, W.; Mettal, U.; Wuisan, Z.G.; Plubrukarn, A.; Ijong, F.G.; Liu, Y.; Schaberle, T.F. A New sesquiterpenoid aminoquinone from an Indonesian marine sponge. *Mar. Drugs* **2019**, *17*, 158. [CrossRef] [PubMed]

26. Neupane, R.P.; Parrish, S.M.; Neupane, J.B.; Yoshida, W.Y.; Yip, M.; Turkson, J.; Harper, M.K.; Head, J.D.; Williams, P.G. Cytotoxic sesquiterpenoid quinones and quinols, and an 11-membered heterocycle, kauamide, from the Hawaiian marine sponge *Dactylospongia elegans*. *Mar. Drugs* **2019**, *17*, 423. [CrossRef] [PubMed]

27. Chen, B.; Zhao, Q.; Gu, Y.-C.; Lan, L.; Wang, C.-Y.; Guo, Y.-W. *Xishielaegans* A–D, sesquiterpene hydroquinones from Xisha marine sponge *Dactylospongia elegans*. *Mar. Drugs* **2020**, *20*, 118. [CrossRef] [PubMed]

28. Ebada, S.S.; de Voogd, N.; Kalscheuer, R.; Müller, W.E.G.; Chaidir, F.; Proksch, P. Cytotoxic drimane meroterpenoids from the Indonesian marine sponge *Dactylospongia elegans*. *Phytochem. Lett.* **2017**, *22*, 154–158. [CrossRef]

29. Mitome, H.; Nagasawa, T.; Miyaoka, H.; Yamada, Y.; van Soest, R.W. Dactyloquinones A and B, new sesquiterpene quinones from the Okinawan marine sponge *Dactylospongia elegans*. *J. Nat. Prod.* **2001**, *64*, 506–5018. [CrossRef] [PubMed]

30. Mitome, H.; Nagasawa, T.; Miyaoka, H.; Yamada, Y.; van Soest, R.W. A new sesquiterpene quinone and other related compounds from *Dactylospongia elegans*. *J. Nat. Prod.* **2003**, *66*, 46–50. [CrossRef] [PubMed]

31. Aoki, S.; Kong, D.; Matsu, K.; Kobayashi, M. Smenospongine, a spongean sesquiterpene aminoquinone, induces erythroid differentiation in K562 cells. *Anti-Cancer Drugs* **2004**, *15*, 363–369. [CrossRef]

32. Yu, H.B.; Yin, Z.F.; Gu, B.B.; Zhang, J.P.; Wang, S.P.; Yang, F.; Lin, H.W. Cytotoxic meroterpenoids from the marine sponge *Dactylospongia elegans*. *Nat. Prod. Res.* **2021**, *35*, 1620–1626. [CrossRef]

33. Zhong, R.; Shao, C.-L.; de Voogd, N.J.; Wang, C.-Y. Sesquiterpene derivatives and steroids from the sponge *Dactylospongia elegans* collected from the south China sea. *Chem. Nat. Compd.* **2014**, *50*, 759–761. [CrossRef]

34. Li, J.; Wu, W.; Yang, F.; Liu, L.; Wang, S.P.; Jiao, W.H.; Xu, S.H.; Lin, H.W. Poloholuanones G–I, dimeric sesquiterpene quinones with IL-6 inhibitory activity from the marine sponge *Dactylospongia elegans*. *Chem. Biodivers.* **2018**, *15*, e1800078. [CrossRef] [PubMed]

35. Yu, H.B.; Gu, B.B.; Iwasaki, A.; Jiang, W.L.; Ecker, A.; Wang, S.P.; Yang, F.; Lin, H.W. Dactylospenes A–E, sesterterpenes from the marine sponge *Dactylospongia elegans*. *Mar. Drugs* **2020**, *18*, 491. [CrossRef] [PubMed]

36. Yu, H.-B.; Gu, B.-B.; Wang, S.-P.; Cheng, C.-W.; Yang, F.; Li, H.-W. New diterpenoids from the marine sponge *Dactylospongia elegans*. *Tetrahedron* **2017**, *73*, 6657–6661. [CrossRef]

37. Li, J.; Wang, Z.; Yang, F.; Jiao, W.H.; Lin, H.W.; Xu, S.H. Two new steroids with cytotoxicity from the marine sponge *Dactylospongia elegans* collected from the South China Sea. *Nat. Prod. Res.* **2019**, *33*, 1340–1344. [CrossRef]

38. Saide, A.; Damiano, S.; Ciarcia, R.; Lauritano, C. Promising activities of marine natural products against *Hematopoietic Malignancies*. *Molecules* **2021**, *9*, 645. [CrossRef] [PubMed]
49. P.

60. Meimetis, L.G.; Nodwell, M.; Yang, L.; Wang, X.; Wu, J.; Harwig, C.; Stenton, G.R.; Mackenzie, L.F.; MacRury, T.; Liang, L.-F.; Poigny, S.; Huor, T.; Guyot, M.; Samadi, M. Synthesis of (+)-hyatellaquinone and (-)-hyatellaquinone.

56. Tasdemir, D.; Bugni, T.S.; Mangalindan, G.C.; Concepcion, G.P.; Harper, M.K.; Ireland, C.M. Cytotoxic bromoindole derivatives of the inositol 5-phosphatase SHIP.

55. Butler, M.S.; Capon, R.J. Beyond polygodial: New drimane sesquiterpene from a Southern marine sponge, Dysidea sp.

52. Boufridi, A.; Lachkar, D.; Erpenbeck, D.; Beniddir, M.A.; Evanno, L.; Petek, S.; Debitus, C.; Poupon, E. Ilimaquinone and 5-epi-ilimaquinone: Beyond a simple diastereomeric ratio, biosynthetic considerations from NMR-based analysis.

57. Kotoku, N.; Nakata, C.; Kawachi, T.; Arai, M.; Kobayashi, M. Concise synthesis and evaluation of effective photoaffinity probe molecule of furospinosulin-1, a hypoxia-selective growth inhibitor from marine sponge.

50. Arai, M.; Kawachi, T.; Setiawan, A.; Kobayashi, M. Hypoxia-selective growth inhibition of cancer cells by furospinosulin-1, a sesquiterpene aminoquinone.

48. Wang, B.; Bai, Z.Q.; Lin, X.P.; Yang, B.; Zhou, X.F.; Liu, Y.H. Chemical constituents of an endophytic fungus.

43. Kong, D.; Aoki, S.; Sowa, Y.; Sakai, T.; Kobayashi, M. Smenospongine, a sesquiterpene aminoquinone from a marine sponge, Spongia sp.

44. Kondracki, M.; Guyot, M. Smenospongine: A cytotoxic and antimicrobial aminoquinone isolated from Spongia sp.

51. Kotoku, N.; Arai, M.; Kawachi, T.; Fujioka, S.; Nakata, C.; Yamada, M.; Kobayashi, M. Studies on analogue synthesis and action-mechanism of furospinosulin-1, hypoxia-selective growth inhibitor from marine sponge.

46. Sumii, Y.; Kotoku, N.; Fukuda, A.; Kawachi, T.; Arai, M.; Kobayashi, M. Structure-activity relationship and in vivo anti-tumor evaluations of dictyoceratin-A and -C, hypoxia-selective growth inhibitors from marine sponge.

54. Butler, M.S.; Capon, R.J. Cometins (A-C), new furanosesterterpenes from an Australian marine sponge, Spongilla sp.

53. Urban, S.; Capon, R.J. Beyond polygodial: New drimane sesquiterpene from a Southern marine sponge, Dysidea sp.

39. Falzone, L.; Salomone, S.; Libra, M. Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. Front. Pharmacol. 2018, 9, 1300. [CrossRef]

42. Amarante-Mendes, G.P.; Rana, A.; Datoguía, T.S.; Hamerschlak, N.; Brumatti, G. BCR-ABL Tyrosine kinase complex signaling transduction: Challenges to overcome resistance in chronic myeloid leukemia. Pharmacutica 2022, 14, 215. [CrossRef] [PubMed]

41. Yan, M.; Liu, Q. Differentiation therapy: A promising strategy for cancer treatment. Chin. J. Cancer 2016, 35, 3. [CrossRef]

20. Falzone, L.; Salomone, S.; Libra, M. Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. Front. Pharmacol. 2018, 9, 1300. [CrossRef]

39. Falzone, L.; Salomone, S.; Libra, M. Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. Front. Pharmacol. 2018, 9, 1300. [CrossRef]