Volume 12, Issue 2, 2025, *107-115*

Jurnal Kesehatan dan Agromedicine

e-ISSN: 2655-7800 | p-ISSN: 2356-332X

https://juke.kedokteran.unila.ac.id/index.php/agro/

Indonesian Marine Natural Product for Anticancer

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Received : 10 Desember 2025 *Accepted : 17 Desember 2025* *Published : 22 Desember 2025*

ABSTRACT: The development of anticancer drugs derived from marine products in Indonesia offers significant promise due to the country's rich marine biodiversity. Marine organisms such as algae, sponges, and marine microorganisms are a valuable source of bioactive compounds with potential anticancer properties. These compounds, including polysaccharides, alkaloids, and peptides, exhibit the ability to inhibit cancer cell proliferation, induce apoptosis, and overcome drug resistance, presenting innovative solutions for cancer treatment. Key marine species being investigated include *Eucheuma sp.*, *Ulva lactuca*, *Gracilaria verrucosa*, *Sargassum polycystum*, and *Ecteinascidia turbinata*, all of which show potent cytotoxicity and diverse mechanisms of action. However, challenges such as sustainable harvesting, compound isolation, and clinical testing must be addressed for these marine products to be successfully developed into therapeutic agents. This paper explores the current state of research on Indonesian marine products as anticancer agents, highlighting their bioactive properties and the opportunities and challenges in advancing these products toward clinical application.
Keywords: anticancer, extract, Indonesia, marine products, secondary metabolite.

Produk Alam Laut Indonesia untuk Antikanker

ABSTRAK: Pengembangan obat antikanker yang berasal dari produk laut di Indonesia menawarkan potensi yang signifikan karena kekayaan keanekaragaman hayati laut yang dimiliki negara ini. Organisme laut seperti alga, spons, dan mikroorganisme laut merupakan sumber berharga senyawa bioaktif yang memiliki potensi sebagai antikanker. Senyawa-senyawa tersebut, termasuk polisakarida, alkaloid, dan peptida, menunjukkan kemampuan untuk menghambat proliferasi sel kanker, menginduksi apoptosis, dan mengatasi resistensi obat, sehingga menghadirkan solusi inovatif untuk terapi kanker. Beberapa spesies laut utama yang sedang diteliti meliputi *Eucheuma sp.*, *Ulva lactuca*, *Gracilaria verrucosa*, *Sargassum polycystum*, dan *Ecteinascidia turbinata*, yang seluruhnya menunjukkan sitotoksisitas kuat dan mekanisme aksi yang beragam. Namun, tantangan seperti pemanenan berkelanjutan, isolasi senyawa, dan uji klinis harus diatasi agar produk laut ini dapat berhasil dikembangkan menjadi agen terapeutik. Makalah ini membahas perkembangan penelitian terkini mengenai produk laut Indonesia sebagai agen antikanker, dengan menyoroti sifat bioaktifnya serta peluang dan tantangan dalam mendorong produk tersebut menuju aplikasi klinis.
Kata kunci: antikanker, ekstrak, Indonesia, produk laut, metabolit sekunder.

DOI : 10.23960/jka.v12i2.pp107-115

INTRODUCTION

The potential of marine natural products from Indonesia for use as cancer drugs is vast and highly promising. While no single marine-derived compound has been definitively proven to cure cancer, scientific research has consistently demonstrated that various marine organisms harbor bioactive compounds with significant anticancer properties. These

compounds could be developed as adjunct therapies to conventional treatments or even serve as foundational components for new cancer chemotherapy drugs [1].

Marine natural products from Indonesia, a country with one of the most biodiverse marine ecosystems in the world, offer immense potential for cancer treatment. Studies have highlighted numerous marine species, including algae, sponges, and marine microorganisms, which contain compounds like alkaloids, terpenoids, and peptides that possess anticancer activity. These compounds can inhibit cancer cell proliferation, induce apoptosis (programmed cell death), and may even help overcome drug resistance, offering an innovative approach to cancer therapy [2–4]

The potential of Indonesia's marine biodiversity for the development of cancer drugs is enormous. As an archipelagic nation located in the heart of the Coral Triangle, Indonesia holds the status as the country with the highest marine biodiversity in the world [5]. This vast and diverse ecosystem represents a "chemical library" that remains largely unexplored. Algae, marine fungi, bacteria, and other marine organisms have been found to produce compounds that exhibit selective toxicity, targeting cancer cells while minimizing damage to normal, healthy cells. This selective cytotoxicity is a critical advantage in reducing the harmful side effects that often accompany conventional chemotherapy treatments, making marine natural products a promising alternative or complementary therapy [6].

The development of marine-derived anticancer drugs is still in its early stages, and many challenges remain. Issues such as the sustainable harvesting of marine organisms, the complexity of isolating and synthesizing bioactive compounds, and the rigorous clinical testing required for drug approval need to be addressed. However, with continued research and investment, Indonesian marine natural products could play a significant role in the future of cancer treatment. This paper aims to explore the potential of Indonesian marine natural products in cancer therapy, highlighting their bioactive properties, the current state of research, and the challenges and opportunities in developing these products for clinical use.

METHODS

The selection method for research articles related to Prospecting Indonesian marine products as anticancer agents was conducted since November 2025 through Indonesian and English language journals. The search strategy used keywords, namely "anticancer", "extract", "marine products", "Indonesia", and "Secondary metabolite." The method used was analytical through the process of collecting relevant data and information regarding the relationship between logical thinking and conclusion-making. Data sources for collecting scientific articles came from Google Scholar, PubMed, Elsevier, NCBI, and health journal websites. Articles were included if they: (1) discussed Indonesian marine organisms with anticancer activity; (2) were original research articles or review articles; (3) were published in English or Indonesian; and (4) were available in full-text format. Articles were excluded if they: (1) were not related to anticancer activity; (2) focused on non-marine organisms; or (3) were abstracts, editorials, or conference summaries without full data. A total of 34 articles met the inclusion criteria and were included in this review.

RESULTS AND DISCUSSION

Marine products possess significant potential as cancer drugs due to the sheer diversity of bioactive compounds they contain, which are capable of fighting cancer cells. This enormous promise is underscored by the rich marine biodiversity of Indonesia, making it a highly valuable natural resource for the discovery of novel drugs. The natural compounds isolated from these organisms can exert their desired anticancer effects through a variety of distinct mechanisms. Several prospective marine species currently being investigated as potent anticancer agents include the algae Cottonii Seaweed and Spinosum Seaweed (*Eucheuma sp*), Sea Lettuce (*Ulva lactuca*), Slender Gracilaria (*Gracilaria verrucosa*), and Sargassum (*Sargassum polycystum*), alongside invertebrates such as

the Mangrove Tunicate (*Ecteinascidia turbinata*) and Sea Hare (*Dolabella auricularia*)

Cottonii Seaweed and **Spinosum Seaweed (*Eucheuma sp.*)**

The genus Eucheuma sp., commonly known as red seaweed, includes key species such as Eucheuma cottonii (also known by its synonym Kappaphycus alvarezii) and Eucheuma spinosum. Both are members of the Solieriaceae family and are widely cultivated in Indonesian waters. The Eucheuma genus holds enormous potential as a source for cancer treatment, and various scientific studies have begun to support this. This red alga is an important source of bioactive compounds (such as polysaccharides, particularly carrageenan, as well as flavonoids and steroids) that are being investigated for novel anticancer therapies. [7].

Eucheuma sp., a red seaweed rich in sulfated polysaccharides (carrageenan and porphyran) and phenolic compounds, exhibits strong anticancer potential through multiple cellular mechanisms. Its sulfated polysaccharides induce apoptosis via the mitochondrial pathway by activating caspase-3 and caspase-9, suppressing Bcl-2 expression, and releasing cytochrome-c. They also modulate immune responses by stimulating macrophages, NK cells, and cytotoxic T cells, while increasing antitumor cytokines such as IL-2 and IFN-γ. Porphyran further inhibits cancer cell proliferation by causing cell cycle arrest at G0/G1 or G2/M through upregulation of p53 and p21 and suppression of cyclin B1 and CDK1[8].

Numerous in vitro (laboratory) studies have demonstrated the effectiveness of Eucheuma cottonii extract in fighting cancer cells. Extracts have shown cytotoxic properties against a range of cancer cells, including cervical (HeLa), colorectal (HCT-116), breast (MCF-7), and lung (A-549) cells. The extract showed particularly strong cytotoxic activity against cervical HeLa cells, with IC50 values recorded at 4.34 µg/mL (ethyl acetate), 4.82 µg/mL (chloroform), 5.73 µg/mL (n-hexane), and 7.54 µg/mL (ethanol) [9]. It also demonstrated significant inhibitory activity against colorectal HCT-116 cells, with the ethyl acetate extract being the most potent at an IC50 of 21.4 µg/mL. Against breast MCF-7 cells, the ethanolic extract showed activity with an IC50 value of 75.7 µg/mL. Weaker, though still present, cytotoxic effects were noted against lung A-549 cells, with IC50 values of 251.73 µg/mL (ethanol) and 261.41 µg/mL (ethyl acetate) [10]. Compounds found in *E. cottonii*, such as flavonoids, steroids, alkaloids, and triterpenoids, are linked to these effects. This includes the reported ability to induce apoptosis (programmed cell death) and potential antimetastatic activity. [11]

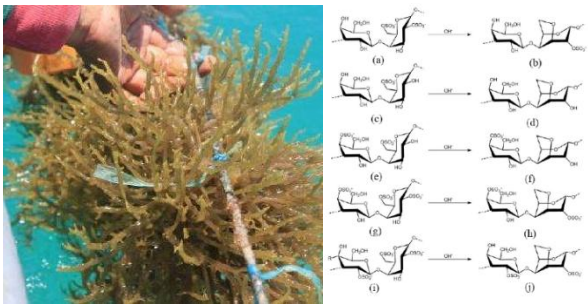


Figure 1. Cottonii Seaweed has Carrageenan as active biomolecules in redseaweed that have potential as anticancer desciptions a) δ-carrageenan; (b) α-carrageenan; (c) γ-carrageenan; (d) β-carrageenan; (e) µ-carrageenan; (f) κ-carrageenan; (g) ν-carrageenan; (h) ι-carrageenan; (i) λ-carrageenan; and (j) θ-carrageenan [8].

Sea Lettuce (*Ulva lactuca*)

One of Indonesia's marine biotas with potential as a source of cancer drugs is the Sea Lettuce (Ulva lactuca), which contains various natural bioactive compounds. Its main compounds, especially sulfated polysaccharides (known as ulvan), as well as phenolic compounds and flavonoids, have been widely studied for their strong bioactivity, including anticancer potential. Sea Lettuce produces these diverse bioactive compounds which demonstrate cytotoxic and anti-proliferative activity against various cancer cells. The potential of the Ulva lactuca species in Indonesia has been investigated, including specimens collected from the waters of Parangtritis Beach, Yogyakarta and Ulee Lheue Beach, Aceh [10,12].

The anticancer mechanism of ulvan, the main sulfated polysaccharide extracted from Sea Lettuce (Ulva lactuca), primarily focuses on inducing programmed cell death and inhibiting cell growth. Ulvan demonstrates cytotoxic activity by triggering apoptosis (programmed cell death) via the intrinsic pathway, which involves increasing the expression of pro-apoptotic proteins such as Bax and the tumor suppressor p53, while simultaneously suppressing anti-apoptotic proteins like Bcl-2. This process leads to the activation of the caspase-9 and caspase-3 cascade, which are the main executioners of cell death. Furthermore, ulvan acts as an anti-proliferative agent by causing cell cycle arrest, thus halting the cancer cell's ability to replicate. This combination of apoptosis induction, proliferation inhibition, and potential immune modulation makes ulvan a promising compound for the development of anticancer therapies [13,14].

Several in vitro (laboratory) and in vivo studies have demonstrated the effectiveness of *Ulva lactuca* (Sea Lettuce) extract in fighting cancer cells. The extracts have shown cytotoxic properties against various cancer cells, including human breast (MCF-7) and colorectal (HCT-116), cancer cells. In in vitro studies, extracts from different solvents showed varied activity against MCF-7 cells: the n-hexane extract was the most potent, with an IC50 value of 45.1 ± 1.7 µg/mL, while the ethyl acetate IC50 147.0±1.9 µg/mL) and ethanol (IC 50 246.8 ± 2.5 µg/mL) extracts showed weaker activity. Against colorectal HCT-116 cells, the n-hexane extract was also active (IC50 69.3 ±1.2 µg/mL) [10].

In vivo, ulvan polysaccharides demonstrated a significant chemopreventive effect against DMBA-induced breast carcinogenesis in a rat model The in vivo study further confirmed these mechanisms, showing that the polysaccharides work by suppressing oxidative stress and inflammation, enhancing the antioxidant defense system, and augmenting apoptosis by increasing p53 expression and decreasing bcl-2 expression [15].

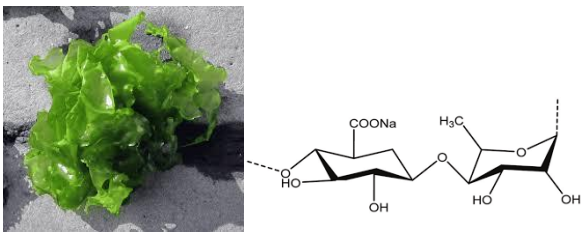


Figure 2. Chemical Structure of Ulvan [16]

Slender Gracilaria (*Gracilaria verrucosa*)

Another of Indonesia's key marine biotas is Slender Gracilaria (*Gracilaria verrucosa*), a species of red algae belonging to the Gracilariaceae family. It is found abundantly in Indonesian waters and has been specifically identified along the Southern Coast of Java, where it grows attached to coral and sand substrates. *Gracilaria verrucosa*, contains various other bioactive compounds such as saponins, flavonoids, and phenolic compounds that are investigated as anticancer agents. Traditionally, this seaweed is often used as a food ingredient, particularly for making jelly [17].

The anticancer mechanism of saponins and phenolic compounds, the primary bioactive compounds extracted from the red seaweed (*Gracilaria verrucosa*), focuses primarily on the induction of programmed cell death and the inhibition of cell viability. *Gracilaria verrucosa* extract exhibits cytotoxic activity by triggering apoptosis (programmed cell death) mainly via the intrinsic (mitochondrial) pathway [18,19]. This mechanism involves the upregulation of the tumor suppressor protein p53, which subsequently increases the ratio of pro-apoptotic proteins such as Bax while downregulating anti-apoptotic proteins like Bcl-2 [20]. This combination of p53/Bax/Bcl-2-mediated apoptosis induction and cell cycle arrest makes G. verrucosa a promising candidate for the development of anticancer therapies.

Several *in vitro* (laboratory) studies have demonstrated the effectiveness of the seaweed extract *Gracilaria verrucosa* in fighting cancer cells. The extracts have shown cytotoxic properties against various cancer cells, including human cervical (HeLa) and colorectal (HCT-116) cancer cells. In *in vitro* studies against HeLa cells, extracts from different solvents showed varied but potent activity: the n-hexane extract was the most

potent, with an IC50 value of 14.94 µg/mL. This was followed by the chloroform (IC50 15.74 µg/mL ethyl acetate (IC50 16.18 µg/mL), and ethanol (IC50 19.43 µg/mL) extracts [19]. Against colorectal HCT-116 cells, the ethanol extract showed the strongest activity (IC50 43.9 µg/mL), while the ethyl acetate (IC50 44.5 µg/mL), chloroform (IC50 44.9 µg/mL), and n-hexane (IC50 49.9 µg/mL) extracts also demonstrated good cytotoxic activity [18].

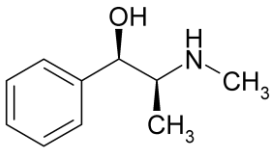


Figure 3. Slender Gracilaria *(Gracilaria verrucosa)* has a potential to be anticancer (Dwi Kurniasari et al., 2018)

Sargassum (*Sargassum polycystum*)

Among Indonesia's vast marine flora, *Sargassum polycystum*, commonly known as Brown Seaweed, is attracting considerable scientific attention for its immediate and demonstrable potential to yield highly effective compounds for cancer treatment. Its main constituents, especially sulfated polysaccharides (known as fucoidans), as well as phenolic compounds, have been widely recognized for their strong biological activities, including significant cytotoxic and anti-proliferative potential against various human cancer cell lines. *Sargassum polycystum* produces these diverse bioactive compounds which exhibit potent anti-tumor effects [21]. The species' potential as an anti-cervical cancer agent has been confirmed through studies on specimens collected from coastal regions of Indonesia.

The anticancer mechanism of fucoidan, the primary bioactive compound extracted from Brown Seaweed (*Sargassum sp*.), focuses primarily on the induction of programmed cell death (apoptosis) and the inhibition of cell proliferation. Fucoidan extract demonstrates cytotoxic activity by triggering apoptosis in breast cancer cells, mainly via the intrinsic (mitochondrial) pathway. This mechanism involves the upregulation of pro-apoptotic proteins such as Bax and Bad, while simultaneously downregulating anti-apoptotic proteins like Bcl-2 and Bcl-xl. This combination of Bax/Bcl-2 ratio-mediated apoptosis induction, cell cycle arrest (specifically at the G0/G1 phase), and anti-metastatic properties makes fucoidan a promising candidate for the development of innovative breast cancer therapies [22].

In vitro studies confirm *Sargassum polycystum* extracts are cytotoxic to human cancer cells, though potency varies by solvent and cell line. Against lung A-549 cells, the n-hexane extract was most potent IC50 21.3 µg/mL, while the ethyl acetate extract was most effective against colorectal HCT-116 cells IC50 26.0 µg/mL [23]. In a separate study on cervical HeLa cells, the chloroform extract showed the strongest cytotoxicity IC50 38.3 µg/mL (A.Arsianti, Bahtiar, et al., 2020). Other extracts, including n-hexane, ethyl acetate, and ethanol, also demonstrated a range of moderate to weak cytotoxic activity against these cell lines.

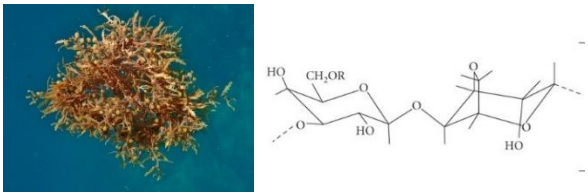


Figure 4. Fucoidan's chemistry structure as anticancer [25]

Mangrove Tunicate (*Ecteinascidia turbinata*)

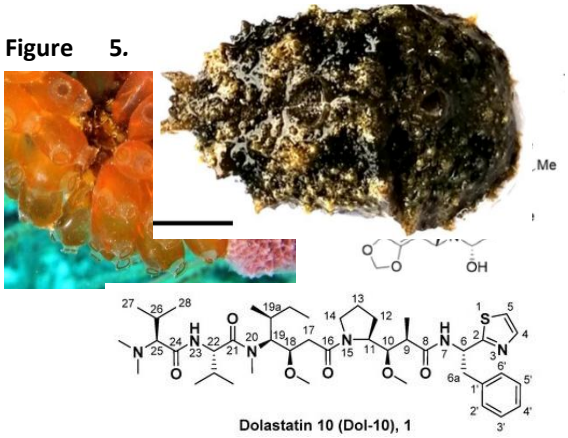
One of Indonesia's marine biotas with proven potential as a source of cancer drugs is the Mangrove Tunicate (*Ecteinascidia turbinata*), which contains a variety of unique bioactive alkaloids. Its main compound, notably Ecteinascidin 743 (ET-743), has been the subject of intensive research and clinical development due to its extremely potent bioactivity. Ecteinascidia turbinata produces this complex compound, which demonstrates potent cytotoxic and antitumor activity against various cancer cells. The potential of *Ecteinascidia turbinata* in Indonesian waters is significant, with specimens found in tropical shallow waters, often attached to mangrove roots in various locations such as the waters of Maluku and Sulawesi [26].

Trabectedin, a marine-derived anticancer agent from *Ecteinascidia turbinata*, demonstrates highly specific mechanisms of

action that distinguish it from conventional chemotherapeutics. One of its most unique features is its ability to irreversibly and covalently bind to duplex stem loops within G-quadruplex (G4) DNA structures, particularly at the N2 position of guanine. This interaction stabilizes G4s, induces transcription-dependent replication stress, and leads to genomic instability in cancer cells, which is a key factor in its potent and selective antitumor effects. In addition to its direct DNA targeting, trabectedin interferes with glutamine metabolism by downregulating the glutamine transporter SLC1A5 and glutamine synthetase, thereby suppressing the escape of cancer stem-like cells from therapy-induced senescence and reducing the population of cells responsible for tumor recurrence [27].

Trabectedin also impairs DNA repair pathways, especially when used in combination with PARP inhibitors or ATR/ATM inhibitors, resulting in synthetic lethality in tumors with DNA repair deficiencies. This combination leads to increased DNA damage, upregulation of pro-apoptotic genes (such as PUMA, NOXA, BAX, and BAK), and cell cycle arrest, ultimately promoting p53-dependent apoptosis [28]. Furthermore, trabectedin modulates the tumor microenvironment by affecting tumor-associated macrophages (TAMs), reducing their immunosuppressive functions, and altering ion channel expression, which contributes to a more favorable immune response against the tumor [29].

Figure 5.



Trabectedin's chemistry structure as anticancer [30]

Sea Hare (*Dolabella auricularia*)

One of Indonesia's most notable marine biotas in anticancer drug discovery is the Sea Hare (*Dolabella auricularia*), which is a source of a series of highly potent bioactive peptides. Its main compounds, particularly Dolastatin 10, have been the subject of decades of global research due to their extraordinary cytotoxic bioactivity. *Dolabella auricularia* (which actually accumulates these compounds from its food source, *cyanobacteria*) contains compounds that demonstrate extremely potent anti-proliferative activity against various cancer cells, even at sub-nanomolar concentrations. This species is widespread in the tropical Indo-Pacific, including in Indonesian waters, making it a highly valuable asset for marine bioprospecting [31].

Dolastatin 10 is a highly potent marine-derived pentapeptide that demonstrates a dual-mechanism anticancer activity. Primarily, it functions as an antimitotic agent by binding to the vinca domain of tubulin, which inhibits microtubule polymerization and disrupts mitotic spindle formation. This action leads to cell cycle arrest at the G2/M phase and induces apoptosis, a process partially amplified by the phosphorylation and inactivation of the BCL-2 protein. Its potency is exceptional, with IC50 values in the sub-nanomolar range, and it is significantly more effective than vinca-alkaloids like vincristine on a molar basis. Beyond this direct cytotoxicity, research shows that dolastatin 10 and its analogs (like MMAE) also have immunomodulatory effects; they promote antitumor immunity by enhancing dendritic cell (DC) maturation and T-cell priming. This dual action provides a clear rationale for combining dolastatin-based therapies with immunotherapies, such as immune checkpoint inhibitors [32].

Figure 6. Dolastatin chemistry structure as anticancer [32].

The development of Indonesian marine plants.

The development of Indonesian marine products as anticancer agents follows a structured and scientifically rigorous process, similar to the development of plant-based drugs, ensuring their efficacy and safety. Indonesia, with its rich marine biodiversity, offers considerable potential for discovering novel anticancer compounds from marine organisms, including seaweeds, marine sponges, and fish species. The development process begins with empirical studies and literature searches, where researchers identify marine organisms traditionally believed to possess medicinal properties or are used in local communities for treating cancer-related symptoms. They also perform thorough reviews of scientific literature and databases to explore the anticancer potential of these marine organisms, such as their ability to inhibit cancer cell proliferation or induce cancer cell death [33]

Once promising marine organisms are identified, researchers extract their bioactive compounds. These compounds are then isolated and chemically analyzed to determine their anticancer activity. The compounds are tested on cancer cell lines in vitro to assess their cytotoxic effects, such as inducing apoptosis or inhibiting the growth of cancer cells. If the in vitro results are promising, further testing is carried out using animal models, such as mice, to evaluate the compound's effectiveness, appropriate dosage, and potential side effects [34]. This stage also includes studying the molecular mechanisms by which these compounds influence cancer cell signaling pathways, helping to better understand their action.

CONCLUSION

Indonesia's marine biodiversity presents a vast and largely untapped resource for the development of novel anticancer agents. The country's rich marine ecosystem, including species such as seaweeds, sponges, and marine microorganisms, harbors a variety of bioactive compounds with significant anticancer potential. These compounds demonstrate the ability to inhibit cancer cell proliferation, induce apoptosis, and modulate immune responses, offering promising alternatives or adjuncts to conventional cancer therapies. Species like *Eucheuma sp.*, *Ulva lactuca*, *Gracilaria verrucosa*, *Sargassum polycystum*, and *Ecteinascidia turbinata* are leading candidates in the search for new anticancer drugs, showing diverse mechanisms of action and potent cytotoxicity against various cancer cell lines.

Despite the promising early-stage findings, there remain several challenges to overcome, including sustainable harvesting practices, efficient extraction methods, and the rigorous testing required for clinical approval. Nevertheless, with continued research and investment in marine bioprospecting, Indonesian marine products could play a pivotal role in the future of cancer treatment. Their development, from laboratory studies to clinical trials, holds the potential to introduce innovative therapies that address current limitations in cancer treatment, such as drug resistance and adverse side effects associated with conventional chemotherapy.

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