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Marine Derived Antimitotic Potential of Lombok Fucus vesiculosus: Dose Dependent Cleavage Arrest in Diadema antillarum Embryos

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ABSTRACT
Brown macroalgae are increasingly investigated as sources of antiproliferative metabolites, but phenotypic evidence linking crude algal extracts to stage-specific mitotic disruption remains limited. This study re-evaluates an exploratory laboratory experiment examining the effect of an ethanol extract of brown alga identified as Fucus vesiculosus from Lombok coastal waters on early development of the sea urchin Diadema antillarum. Adult sea urchins were conditioned separately by sex; gametes were obtained and fertilized, and embryos were exposed to five extract concentrations (1.0, 2.5, 4.0, 5.0, and 5.5 mg/100 mL). Twenty embryos were followed per condition, with progression assessed from zygote through cleavage, blastula, gastrula, and pluteus stages. A clear concentration-dependent loss of developmental progression was observed. At 1.0 mg/100 mL, 90% of embryos reached the 32-cell stage but none progressed to blastula. At 2.5 mg/100 mL, 60% reached 16 cells and development stopped before 32 cells. At 4.0 mg/100 mL, only 25% reached 8 cells. At 5.0 and 5.5 mg/100 mL, only 10% and 5%, respectively, reached the 8-cell stage, with arrest apparent from the earliest cleavages. These staged phenotypes support a dose-responsive antimitotic or embryotoxic effect of the crude ethanol extract. Updated evidence on fucoidan- and phlorotannin-rich F. vesiculosus preparations provides biological plausibility through cell-cycle arrest, apoptosis, and suppression of proliferative signaling. However, because the extract was not chemically standardized and the assay was descriptive, the results should be interpreted as a phenotypic screening signal rather than proof of anticancer efficacy. The principal novelty is the demonstration of a graded cleavage-stage arrest pattern in D. antillarum across five extract doses using locally sourced material, providing a foundation for modern fractionation, molecular identification, and mechanism-focused validation.

INTRODUCTION

Marine macroalgae are a chemically diverse source of sulfated polysaccharides, phlorotannins, pigments, sterols, and terpenoids with increasingly well-characterized antiproliferative properties. Contemporary reviews place brown algae among the most promising marine resources for oncology-oriented natural-product discovery because several of their metabolites can influence cell proliferation, apoptosis, angiogenesis, oxidative stress, and immune signaling (Jin et al., 2022; Frazzini & Rossi, 2025). Among these compounds, fucoidans are fucose-rich sulfated polysaccharides whose anticancer activity has been investigated in both cell-based and animal models, whereas phlorotannins represent a structurally distinct polyphenolic class with tumor-selective cytotoxic effects reported for Fucus-derived preparations (Catarino et al., 2021; Cao et al., 2021).

Fucus vesiculosus is particularly relevant because both its polysaccharide and polyphenolic fractions have been associated with suppression of proliferation. Fucoidan from F. vesiculosus has been reported to induce cell-cycle arrest and apoptosis in experimental cancer models, and recent work indicates that the magnitude of activity depends strongly on extraction conditions, molecular weight, sulfate content, and accompanying phlorotannins (Chantree et al., 2021;

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Zahariev et al., 2023; Obluchinskaya et al., 2025). In neuroblastoma cells, F. vesiculosus fucoidan recently reduced proliferation while attenuating growth-factor signaling without simply producing nonspecific acute cell death, underscoring the mechanistic diversity of these preparations (Weber et al., 2025).

The sea urchin embryo offers a complementary phenotypic system for detecting compounds that interfere with fertilization, cleavage, spindle function, DNA replication, and early morphogenesis. Its rapid and synchronous development permits direct visualization of stage-specific developmental failure. Sea urchin embryo assays remain widely used in toxicological screening, and recent evaluations emphasize their sensitivity to developmental perturbation and the need to control solvent-related effects (Semenova et al., 2024; Burić et al., 2025). For an exploratory antimitotic screen, a concentration-related shift from late-stage arrest to early cleavage arrest can provide a visually interpretable biological signal before compound-level mechanism studies are undertaken.

The original experiment underlying this manuscript tested an ethanol extract of brown alga identified as F. vesiculosus collected from Lombok coastal waters against D. antillarum embryos. The historical report documented a graded reduction in cleavage progression across five concentrations but interpreted the findings using literature that is now outdated. The present article reframes those observations using current evidence from 2021–2026 and emphasizes what can, and cannot, be concluded from the model. The novelty lies in mapping the extract effect across sequential cleavage stages in D. antillarum rather than reporting a single endpoint, thereby generating a dose-stage phenotype that can guide fractionation and mechanistic follow-up. The objective was to characterize the pattern of developmental arrest caused by the ethanol extract and to contextualize its antimitotic potential against contemporary evidence on F. vesiculosus bioactives.

MATERIALS/METHODS

Study design and setting. The underlying work was an exploratory laboratory experiment conducted at Poltekkes Kemenkes Mataram over five months (June–October 2010). Algal material was collected from coastal sites at Grupuk (Central Lombok) and Ekas (East Lombok), while adult D. antillarum were obtained from Grupuk and Sire coastal waters. The article reports the original experimental observations while updating only the scientific framing and literature context; no new wet-laboratory experiments were performed for this manuscript.

Preparation of the algal ethanol extract. Approximately 5 kg of collected algal material was dried at room temperature for five days, reweighed, and ground to produce a dry powder. The material was macerated with 96% ethanol for repeated 3 × 24 h extraction cycles, filtered under vacuum, and concentrated using a rotary evaporator. Additional ethanol extraction was continued until the filtrate became clear. The concentrated residue was treated as 100% crude ethanol extract. Because the original study did not quantify fucoidan, phlorotannins, sulfate content, molecular weight distribution, or other metabolites, the tested material is appropriately described as a crude ethanol extract rather than a purified fucoidan preparation.

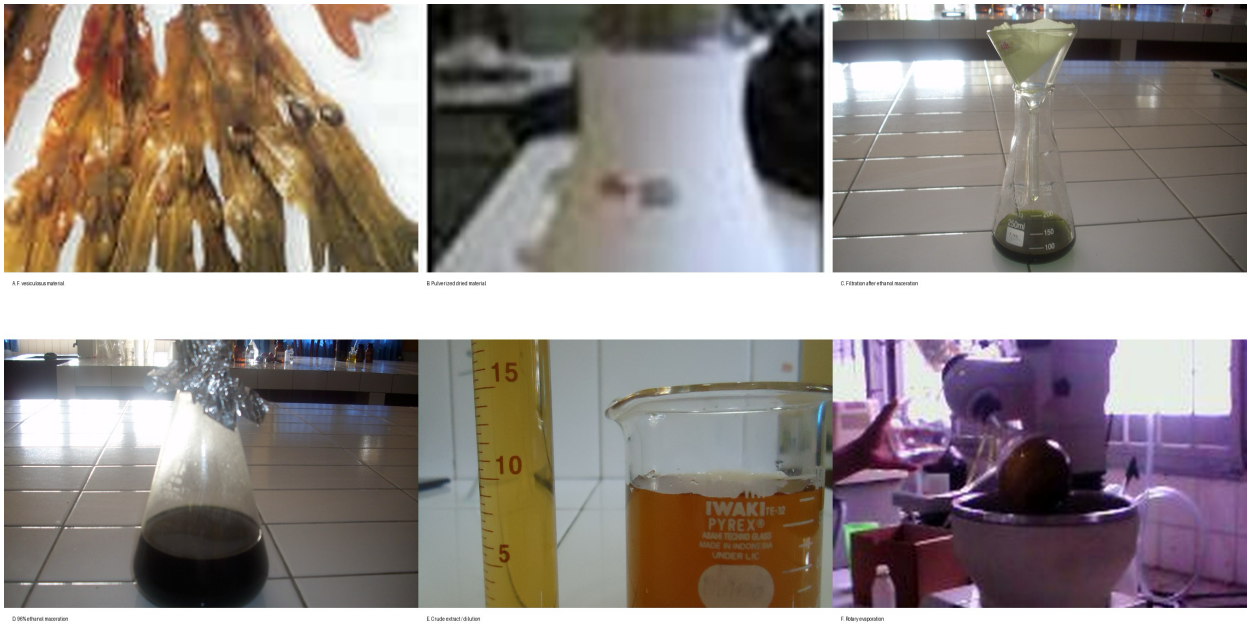


Figure 1. Intervention workflow documented in the original study: algal material preparation, ethanol maceration/filtration, concentration, and preparation of crude extract for embryo exposure. Photographs are reproduced from the original research archive.

Sea urchin conditioning, gamete handling, and exposure. Five male and five female adult sea urchins were maintained separately in seawater aquaria before the assay. Eggs and sperm were obtained from mature animals and used for fertilization. The experimental concentration series was selected from a preliminary exploration and comprised 1.0, 2.5, 4.0, 5.0, and 5.5 mg extract per 100 mL. For each exposure level, 20 embryos were observed in parallel with a negative-control condition. The developmental sequence recorded in the study was: egg + sperm, fertilized zygote, 2-cell, 4-cell, 8-cell, 16-cell, 32-cell, blastula, gastrula, and pluteus.

Outcome assessment. The primary phenotypic outcome was the number and percentage of embryos that successfully reached each developmental stage at the scheduled observation time (zygote at approximately 15 min; 2-cell at 60 min; 4-cell at 90 min; 8-cell at 2 h; 16-cell at 2.5 h; 32-cell at 15 h; blastula at 24 h; gastrula at 2 days; and pluteus at 5 days). The original experiment was descriptive and did not report independent replicate-level variance or inferential statistical testing. Accordingly, this manuscript does not retrospectively assign p values or confidence intervals that were not generated in the original dataset.

Interpretive framework. Contemporary sea urchin literature supports the use of cleavage arrest and developmental abnormalities as sensitive phenotypic endpoints, while also showing that solvents can themselves alter embryogenesis at sufficient concentrations (Semenova et al., 2024; Burić et al., 2025). Since the crude extract was produced in ethanol but the final test preparation was diluted and the original report did not provide a matched residual-ethanol concentration, the observed effects are interpreted as extract-associated rather than compound-specific. This limitation is explicitly considered in the discussion.

RESULTS AND DISCUSSION

Dose-dependent loss of cleavage progression. The negative control maintained 100% progression through the observed developmental stages. In contrast, all extract concentrations reduced subsequent development, and the stage at which arrest became evident shifted progressively earlier as concentration increased. This pattern is summarized in Table 1 and Figure 2.

Table 1. Percentage of embryos reaching sequential developmental stages at each extract concentration. Values are derived from the original count of 20 embryos per condition.

Dose (mg/100 mL)	Zygote %	2-cell %	4-cell %	8-cell %	16-cell %	32-cell %	Blastula %	Dominant phenotype
Control	100	100	100	100	100	100	100	No arrest in observation window
1.0	100	100	90	90	90	90	0	Reached 32-cell; no blastula
2.5	100	100	80	70	60	0	0	Arrest before 32-cell
4.0	100	70	50	25	0	0	0	Arrest after 8-cell
5.0	100	50	10	10	0	0	0	Early cleavage arrest
5.5	100	25	5	5	0	0	0	Strongest early cleavage arrest

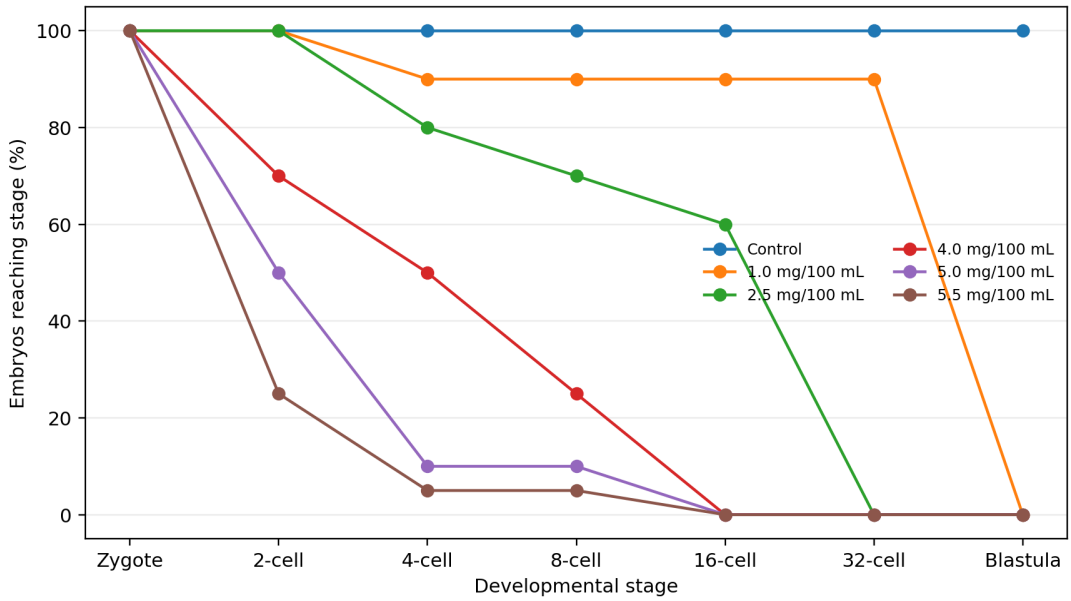


Figure 2. Dose-stage response of D. antillarum embryos exposed to crude F. vesiculosus ethanol extract. Increasing concentration shifted the developmental endpoint from late cleavage (32-cell) toward early cleavage arrest.

At 1.0 mg/100 mL, fertilization and the 2-cell stage remained comparable with control, but only 18 of 20 embryos (90%) reached the 4-, 8-, 16-, and 32-cell stages. None reached blastula at 24 h. This is important because the lowest tested concentration did not primarily prevent fertilization; instead, it permitted several cleavage cycles before developmental progression collapsed. Such a delayed phenotype is compatible with an antiproliferative or cumulative embryotoxic effect rather than immediate gamete lethality.

At 2.5 mg/100 mL, 80% reached the 4-cell stage, 70% reached 8 cells, and 60% reached 16 cells, but no embryos progressed to 32 cells. At 4.0 mg/100 mL the response became markedly earlier: only 70% reached 2 cells, 50% reached 4 cells, and 25% reached 8 cells, with no progression to 16 cells. The two highest concentrations produced the strongest early-cleavage phenotype. At 5.0 mg/100 mL, 50% reached 2 cells and only 10% reached 4 and 8 cells; at 5.5 mg/100 mL, the corresponding values were 25%, 5%, and 5%. Thus, the dataset shows both a reduction in the proportion of embryos completing cleavage and a leftward shift in the arrest point as dose increases.

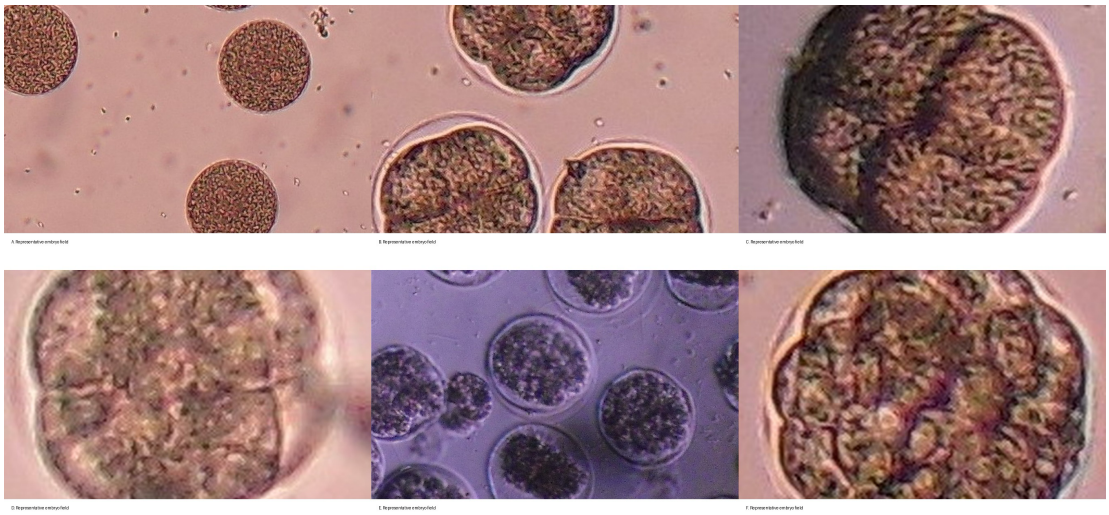


Figure 3. Representative embryo micrographs from the original study archive showing cleavage-stage morphology observed during the intervention experiment. Because the archived micrographs were not individually stage-annotated in the source file, the panels are presented as representative fields rather than as independently verified stage labels.

The dose-stage pattern is biologically plausible in light of current research on F. vesiculosus. Fucoidan can suppress proliferation through cell-cycle regulation, while Fucus-derived phlorotannin-rich fractions can activate apoptosis and necrosis in gastrointestinal tumor cell lines (Catarino et al., 2021). In cholangiocarcinoma cells, F. vesiculosus fucoidan has been reported to reduce viability and promote cell-cycle arrest and mitochondria-related apoptosis (Chantree et al., 2021). More recent reviews synthesize similar findings across tumor systems and identify cell-cycle arrest, apoptosis, anti-angiogenic activity, and modulation of signaling pathways as recurring mechanisms (Jin et al., 2022; Bhuyan et al., 2023; Zahariev et al., 2023). These modern data do not prove that the same molecular pathway caused the sea urchin phenotype, but they strengthen the rationale for considering the crude extract as a source of antiproliferative metabolites.

A second point of convergence is the concentration dependence. The original embryo assay showed progressively earlier arrest with increasing extract dose. Contemporary extraction research demonstrates that F. vesiculosus preparations can differ substantially in fucoidan yield, molecular weight, sulfate content, and phlorotannin content, and that these compositional differences translate into distinct antioxidant and anticancer activity (Obluchinskaya et al., 2025). This makes it unlikely that "F. vesiculosus extract" should be treated as a chemically uniform intervention. The sharp dose-response observed here is therefore best viewed as the integrated effect of a crude mixture whose active constituents remain unresolved.

The strongest phenotype at 5.0–5.5 mg/100 mL began during the first cleavage interval. This is particularly informative because early sea urchin cleavage depends on precisely coordinated DNA replication, centrosome function, spindle assembly, chromosome segregation, and cytokinesis. A recent review of sea urchin toxicology confirms that embryotoxicity assays dominate contemporary sea urchin testing because early developmental stages rapidly expose perturbations that may not be obvious in adult organisms (Burić et al., 2025). Likewise, Semenova et al. (2024) demonstrated that the sea urchin embryo can distinguish cleavage arrest from later developmental abnormalities and stressed the importance of solvent controls. The present data therefore provide a valid phenotypic signal of disrupted early development, even though they cannot identify the molecular target.

The updated literature also supports restraint in using the term "anticancer." A systematic review and meta-analysis of animal experiments reported overall antitumor activity of fucoidan, but emphasized heterogeneity in models, preparations, doses, and study quality (Cao et al., 2021). Reviews published since then similarly conclude that macroalgal compounds are promising preclinical candidates rather than established anticancer drugs (Jin et al., 2022; Frazzini & Rossi, 2025). Accordingly, the current sea urchin assay should be described as an antimitotic or antiproliferative phenotypic screen. It demonstrates interference with cell division in a non-mammalian embryo, not selective toxicity toward malignant human cells.

This distinction is particularly important because the crude extract may contain fucoidan, phlorotannins, pigments, sterols, and other metabolites with overlapping or opposing effects. In 2025, Weber et al. showed that F. vesiculosus fucoidan reduced proliferation of neuroblastoma cells while attenuating HGF, IGF2, and VEGF signaling, illustrating that growth suppression can occur through signaling modulation rather than nonspecific cytotoxicity. Conversely, purified Fucus-derived phlorotannin fractions have demonstrated direct tumor-cell death signaling (Catarino et al., 2021). Without fractionation and chemical profiling, the embryo arrest observed here could reflect one dominant constituent, several synergistic constituents, or general toxicity of the mixture.

The observed lack of blastula formation at even the lowest concentration is also notable. At 1.0 mg/100 mL, embryos that reached the 32-cell stage failed to proceed to blastula, suggesting that the extract may affect not only the mechanics of cleavage but also later developmental processes required for compaction, blastocoel formation, or continued proliferative competence. At higher doses, these later phenotypes are masked by earlier arrest. This hierarchical dose-stage pattern is a useful feature of the dataset because it can guide future mechanism experiments: lower concentrations may be more informative for post-cleavage developmental pathways, whereas higher concentrations are more appropriate for analyzing immediate cell-cycle failure.

From a marine-bioprospecting perspective, the present findings are relevant because they connect an underutilized coastal biological resource with a directly observable cell-division phenotype. Marine natural products remain a major source of structurally diverse pharmacophores, and recent reviews emphasize that algae contribute polysaccharides, polyphenols, terpenoids, sterols, pigments, and other metabolites capable of modulating proliferation, apoptosis, angiogenesis, and cell-cycle control (Liao et al., 2024; Santhiravel et al., 2025; Alves & Diederich, 2025). Brown macroalgae are particularly attractive because their chemistry reflects adaptation to high salinity, ultraviolet exposure, hydrodynamic stress, and fluctuating environmental conditions. These ecological pressures are associated with chemically distinctive secondary metabolites that can provide starting points for pharmacological discovery. In this context, the Lombok coastal material is not merely a botanical source used for an embryo assay; it represents a locally

available marine-resource platform that can be developed through taxonomic confirmation, standardized extraction, bioassay-guided fractionation, and compound-level characterization.

F. vesiculosus deserves particular attention within this marine-resource framework. Modern studies show that its biological activity cannot be attributed to a single constituent. Fucoidan, a sulfated fucose-rich polysaccharide abundant in brown algal cell walls, has repeatedly been linked with suppression of tumor-cell proliferation, induction of apoptosis, interference with growth-factor signaling, and cell-cycle arrest (Jin et al., 2022; Zahariev et al., 2023; Weber et al., 2025). At the same time, F. vesiculosus-derived phlorotannins can exert direct antitumor effects; Catarino et al. (2021) demonstrated that phlorotannin-rich fractions reduced viability of gastric and colorectal tumor cells and activated apoptotic and necrotic pathways while showing lower toxicity toward non-tumor cells. Thus, the crude ethanol extract used in the present work plausibly contained a multi-component chemical system in which polyphenolic and other ethanol-soluble metabolites could act together with residual polysaccharide-derived fractions. The important point for the current study is not to assign the embryo phenotype prematurely to fucoidan or phlorotannins, but to show that the observed antimitotic signal is consistent with the known antiproliferative repertoire of F. vesiculosus.

The stage-specific nature of the response provides stronger biological justification than a simple end-point statement that the extract was 'toxic'. At 1.0 mg/100 mL, embryos retained the capacity to undergo repeated cleavage and reached the 32-cell stage, yet failed to form blastulae. At 2.5 mg/100 mL, the terminal developmental point shifted to 16 cells, whereas concentrations of 4.0-5.5 mg/100 mL produced arrest around the 8-cell stage or earlier. This ordered leftward displacement of the terminal stage as concentration increased indicates a graded perturbation of proliferative capacity. Antimitotic agents classically produce concentration-dependent failure of cell-cycle progression by disturbing microtubule dynamics, spindle assembly, chromosome segregation, DNA replication, checkpoint control, or cytokinesis. The present assay cannot identify which of these processes was affected; nevertheless, the orderly dose-stage relationship is more compatible with a biologically active antiproliferative mixture than with a random pattern of developmental failure. This interpretation is also aligned with contemporary marine anticancer literature, in which structurally diverse marine metabolites act through multiple targets rather than a single universal pathway (Liao et al., 2024; Alves & Diederich, 2025; Liu et al., 2026).

Comparison with recent F. vesiculosus studies further strengthens the interpretation. Weber et al. (2025) reported that F. vesiculosus fucoidan reduced neuroblastoma-cell proliferation and attenuated HGF-, IGF2-, and VEGF-related growth signaling. This observation is relevant because it shows that a Fucus-derived preparation can inhibit proliferative behavior without requiring immediate nonspecific cell destruction. Catarino et al. (2021), using a different chemical fraction, showed activation of programmed cell-death pathways in gastrointestinal tumor cells. These two findings illustrate complementary mechanisms - growth suppression and cell death - that may coexist in complex algal extracts. The present D. antillarum phenotype similarly appears concentration dependent: lower concentrations allowed several rounds of cleavage before developmental competence was lost, whereas higher concentrations produced much earlier arrest. Such a pattern provides a rationale for future fractionation experiments in which low-dose delayed arrest and high-dose early arrest are tested separately, potentially revealing fractions that preferentially perturb proliferation rather than cause generalized cytotoxicity.

The marine origin of the tested material also adds translational and regional significance. Current pharmacognosy increasingly recognizes marine ecosystems as reservoirs for drug leads that are chemically distinct from terrestrial natural products (Santhiravel et al., 2025). Recent reviews of brown-algal bioactives describe these organisms as underused sources of antiproliferative compounds and explicitly call for integrated extraction optimization, metabolomics, structural characterization, and mechanism-based validation (Liao et al., 2024; Sahoo et al., 2025). The Lombok coastline contains extensive and comparatively underexplored marine biodiversity; therefore, a reproducible antimitotic signal from a locally collected brown alga can be viewed as an entry point for regional blue-biotechnology research. The value of the present finding lies less in claiming an immediately usable anticancer agent and more in identifying a local marine biomass with a measurable dose-dependent biological phenotype that merits systematic chemical and pharmacological follow-up.

This positioning is important for defining novelty. Many contemporary publications on macroalgae summarize anticancer mechanisms in established mammalian cell lines, while this work provides a sequential, visually resolved developmental phenotype in D. antillarum embryos. The five-level concentration series allows the biological effect to be mapped across multiple cleavage stages rather than reduced to a single percentage of viable cells. In screening terms, this creates a phenotypic fingerprint: late cleavage failure at the lowest dose, intermediate-stage arrest at 2.5 mg/100 mL, and strong early-cleavage inhibition at 4.0-5.5 mg/100 mL. The combination of locally sourced marine material, stage-resolved embryo observations, and a coherent concentration-response gradient constitutes the principal

novelty of the dataset. It also provides an experimentally efficient basis for prioritizing active fractions before moving to more expensive mammalian cancer models.

At the same time, the updated literature clarifies the level of claim that is scientifically defensible. Reviews from 2024-2026 consistently describe marine algae and marine natural products as promising sources of anticancer leads, but they also emphasize heterogeneity of extracts, incomplete structure-activity relationships, and the need for rigorous preclinical validation (Liao et al., 2024; Frazzini & Rossi, 2025; Santhiravel et al., 2025; Liu et al., 2026). Accordingly, the term 'antimitotic potential' is more appropriate here than 'anticancer efficacy'. The embryo assay demonstrates interference with rapid cell division, which is a biologically relevant property for antimitotic screening, but it does not establish tumor selectivity, pharmacokinetics, therapeutic index, or efficacy in humans. Framing the result in this way actually strengthens its scientific contribution by linking the historical observation to a modern drug-discovery pipeline without overstating what the experiment proves.

The novelty of this study should therefore be framed around phenotype resolution rather than molecular mechanism. Within the original dataset, five graded concentrations were linked to distinct terminal developmental stages: 32 cells at 1.0 mg/100 mL, 16 cells at 2.5 mg/100 mL, and predominantly 8 cells or earlier at 4.0–5.5 mg/100 mL. This stage-resolved pattern provides more information than a single viability endpoint and creates a practical roadmap for modern validation. A contemporary follow-up could couple live-cell microscopy with tubulin immunofluorescence, DNA-content analysis, caspase assays, and targeted chemical profiling to distinguish spindle disruption, replication stress, apoptosis, and nonspecific toxicity.

Several limitations materially affect interpretation. First, the experiment was exploratory and descriptive, with 20 embryos counted per condition and no reported independent biological replicate structure; consequently, precision estimates and inferential comparisons cannot be reconstructed. Second, the crude extract was not chemically standardized, and the original report did not quantify residual ethanol in the final exposure medium. Third, the algal identification recorded in the historical study was not accompanied by a preserved voucher specimen or molecular barcode in the available report. Because chemical composition and even species assignment can influence biological activity, modern replication should include taxonomic authentication and metabolomic characterization. Fourth, the study predates current reporting expectations, and key variables such as randomization, blinding, exact spawning induction procedure, and batch-to-batch extraction variability were not documented in sufficient detail.

These limitations do not eliminate the value of the result; rather, they define its appropriate role. The data provide a visually coherent, concentration-dependent screening signal that is consistent with the contemporary biological plausibility of F. vesiculosus-derived antiproliferative compounds. The next step is not to infer clinical anticancer efficacy but to identify which extract fractions reproduce the cleavage-arrest phenotype and whether those fractions selectively inhibit proliferating mammalian tumor cells while sparing non-malignant cells.

CONCLUSIONS

Crude ethanol extract of brown alga identified as Fucus vesiculosus produced a clear dose-dependent inhibition of D. antillarum embryonic development. Increasing concentration shifted developmental arrest from the 32-cell stage at 1.0 mg/100 mL to the 16-cell stage at 2.5 mg/100 mL and to the 8-cell stage or earlier at 4.0–5.5 mg/100 mL. Updated literature on fucoidan and phlorotannins supports the biological plausibility of an antiproliferative effect, but the present experiment does not establish a specific molecular mechanism or human anticancer efficacy. Its strongest contribution is the stage-resolved dose-response phenotype, which provides a rational basis for modern chemical fractionation, molecular target studies, and confirmatory tumor-cell assays.

RECOMMENDATIONS FOR FUTURE WORK

Future studies should (1) authenticate the algal specimen by voucher deposition and molecular barcoding; (2) standardize extraction and quantify fucoidan, sulfate, phlorotannins, and major metabolites; (3) include vehicle controls matched for residual solvent; (4) use replicated embryo batches from multiple adults with blinded scoring; (5) calculate concentration-response parameters such as EC50 for cleavage arrest; and (6) validate active fractions in mammalian cancer and non-malignant cell lines using cell-cycle, apoptosis, spindle, and proliferation assays. These steps would convert the present phenotypic signal into a reproducible mechanism-oriented natural-product program.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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