RESEARCH PAPER

Therapeutic Efficacy of *Holothuria atra* extract against Estradiol-Induced Pituitary Cancer in Adult Female Albino Rats

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Abstract

Background: Pituitary tumors include adenomas, carcinomas, and craniopharyngiomas and the most common rats are prolactinomas. This paper aimed at determining the antitumor activity of sea cucumber extract (SCE) in relation to Estradiol induced pituitary cancer in female albino rats. Methods: Four groups (n = 8/group) were randomly formed from adult female albino rats (150–180 g): (1) control, (2) SCE-treated healthy rats (10 mg/kg/day, via intraperitoneal injections, for 6 weeks), (3) Estradiol-induced pituitary cancer group, and (4) Estradiol-induced rats treated with SCE (10 mg/kg/day, via intraperitoneal injections, for 6 weeks). Findings: The administration of SCE markedly reduced Estradiol-induced changes, as suggested by the lowered serum levels of CEA, CA19.9, TNF-α and IL-1β. Furthermore, SCE restored oxidative balance by decreasing MDA and NO levels whilst augmenting SOD activity and GSH and CAT concentrations in serum. Conclusion: These results demonstrate sea cucumber extract chemopreventive potential against Estradiol-induced pituitary tumorigenesis, most likely via its immunomodulatory, anti-inflammatory, and antioxidant qualities.

- **Keywords:** Pituitary cancer, Sea Cucumber Extract, Estradiol, antitumor, Rats.

How to cite this article: Ibrahim H.M. Mostfa, Mohammed Abdel-Wahab, Hussam Askar, and Mahmoud Ashry. Therapeutic Efficacy of Holothuria atra extract against Estradiol-Induced Pituitary Cancer in Adult Female Albino Rats. Int J Drug Deliv Technol. 2026;16(76s):1946-1954. DOI: 10.25258/ijddt.16.76s.185.

Introduction

The pituitary gland becomes responsive to intricate peripheral and central cues through two mechanisms. To keep homeostasis in place, trophic hormone release is first held under precise control. Second, developmental or acquired pituitary signals may provoke plastic pituitary growth responses, which take the form of hypoplasia, hyperplasia, or adenoma formation. Such clinically evident pituitary mass plastic changes are the evidence of either physiologic or pathologic reaction to extrapituitary or intrapituitary signals. Functional defects of the hormone secretion commonly go hand in hand with the pituitary proliferative alterations, resulting in the syndromes of hormone deficiency or excess (Melmed, 2003).

Prolonged administration of estrogen has been shown to cause prolactin (PRL) cell hyperplasia and tumors in male and female rats. Pituitary hyperplasia and spontaneous pituitary tumors are also prevalent in certain strains of aging rats. A major problem with the use of spontaneous pituitary tumor development in aging rats as an animal model for the study of pituitary neoplasms is that the percentage of tumors and the time course of tumor development are difficult to control. Thus the use of a model that results in hyperplasia and tumors in animals within a relatively short period provides an experimental model that is more reproducible. This has been achieved in certain strains of rats by administration of estrogens.4-9 Most of the lesions that develop after estrogen treatment have been called tumors, and a distinction between

PRL cell hyperplasia and tumors has not been carefully examined except for a few reports in aging rats with spontaneous pituitary lesions.1

The challenging conditions of the marine environment, such as temperature shifts, high salinity, pressure, and limited light, shape the unique biochemistry of marine organisms, etc (Dyshlovoy *et al.,* 2015 and Dyshlovoy *et al.,* 2020). Such adaptations cause a variety of bioactive compounds to be formed and thus marine life is a promising source of developing drugs and biotechnological innovations (Dehghani et al., 2022; Mayer *et al.,* 2017; Brunt *et al.,* 2018). About 15 to 20 compounds produced from marine sources have been authorized for clinical use thus far, and they are used to treat ailments like heart disease, cancer, pain, and viral infections. Some of these drugs are designed to specifically target cancer cells by linking the active compound to an antibody, improving precision and effectiveness (Francesch *et al.,* 2024 and Dyshlovoy *et al.,* 2020). Compounds of marine origin still promise new vistas in neurological disorders treatment, cancer as well as the creation of new antibiotics (Abuzahrah et al., 2025; Silva et al., 2024). Their varied mechanisms and capacity to specifically target cancer cells offer promising avenues for novel and efficient treatments, despite the difficulties associated with clinical use (Al-Hussaniy et al., 2025).

In the present context, in addition to land sources of natural products, marine organisms (microorganisms, vertebrates, invertebrates and algae) are also starting to attract attention as sources of pharmacologically active substances in the research (Gong et al., 2018). There is a dire need to advance the research on marine bioactives in both conventional and contemporary systems because of burgeoning frequency of infections, changes in metabolism, and age/lifestyle related diseases (Nii-Trebi, 2017). Biologically active peptides, fatty acids, pigments, alkaloids and polysaccharides, among other chemical compounds, have been discovered earlier in marine sources, and their bioprospection is one of the ways of designing potential anticancer drugs. Specifically, there has been a gigantic growth in awareness of anticancer applications of holothurians (Echinodermata, Holothuroidea), otherwise known as the sea cucumbers, in the last 20 years. It is due to these discoveries that the sea cucumber, which is a sea creature, has taken the centre stage of the scientific fraternity because of its high nutritional content and potential treatment of cancer (Khotimchenko, 2015). One of the most promising groups is the sea cucumbers (class Holothuroidea). There are about 1,716 species globally, widely distributed through the ocean, of these leathery skinned, elongated bodied, single branched gonad invertebrates, and the Asia-Pacific boasts the most biodiversity (Pangestuti et al., 2018). Sea cucumbers are widespread in the oceans of the world, and the Red Sea of Egypt is inhabited by over 20 sea cucumber species, including *Holothuria atra* and *Synapta maculata*, that clean the reefs and represent an important ecological component.

The environment that the sea cucumbers are exposed to has resulted in the evolution of the unique secondary metabolites that generate the biological activity (Bahrami et al., 2014). Since ancient times sea cucumbers have been valued with regard to their medicinal properties. The Ming dynasty record (1368–1644) refers to sea cucumbers as “haishen,” or “ocean ginseng,” because they shared the medicinal properties of ginseng (Bahrami et al., 2014). In the Traditional Chinese Medicine system, sea cucumbers have found application as a rejuvenating agent for skeletal and joint weakness, particularly that of old age inflexibility, malfunctioning of the renal system, sexual dysfunctions, dry stool constipation, lipid digestive difficulties, and circulatory dysfunctions (Gopakumar and Gopakumar 2020).

Sea cucumbers are producers of various biocompounds such as triterpene glycosides (saponins), polysaccharides, proteins, peptides and phenolics (Choo, 2008; Ahmad et al., 2020). Among these, triterpene glycosides—the characteristic secondary metabolites of the group—are the most widely investigated for anticancer activity, showing hemolytic, cytotoxic and antifungal effects through membranotropic action (Choo, 2008). These compounds inhibit human tumor cell growth in vitro and lower tumor burden and metastasis when given by the intraperitoneal route in rodents (Aminin et al., 2015).

The anticancer effects of sea cucumber compounds involve induction of apoptosis through the caspase pathway, cell cycle arrest (S or G2/M stage), modulation of NF-κB, and control of cancer-related proteins such as EGFR, Akt, ERK, FAK and MMP-9 (Aminin et al., 2015; Adrian and Collin, 2018; Zare et al., 2023). Through them, cell adhesion, migration, angiogenesis and tumor invasion all fall away, and growth of the tumor is strongly suppressed both in vitro and in vivo (Aminin et al., 2015; Adrian and Collin, 2018; Zare et al., 2023).

The initial observations of anticancer activity of sea cucumber glycosides occurred in 1952 when Nigrelli observed that holothurin of *Actinopyga agassizi* could be used to inhibit tumor growth in Sarcoma-180 in mice (Nigrelli, 1952), and subsequently, activity in epidermal carcinoma cells (Friess et al., 1960; Nigrelli et al., 1967) was reported. A few potent compounds have been also found in more recent studies: Philinopside A of *Pentacta quadrangularis* is a dual anti-angiogenic and anti-tumor receptor tyrosine kinase inhibitor (Tong et al., 2005); Echinoside A of *Holothuria nobilis* targets topoisomerase 2α (Li et al., 2010); Frondoside A of *Cucumaria frondosa* is an agent against pancreatic, breast, lung and prostate cancers and free of toxicity (Al Marzouqi et al., 2011; Attoub et al., 2013); and Stichoposide C of *Thelenota anax* is an apoptotic activator by ceramide generation (Yun et al., 2012).

Also, triterpene glycosides are able to reverse P-glycoprotein-mediated multidrug resistance, increasing the effectiveness of chemotherapy (Aminin et al., 2014; Menchinskaya et al., 2013). Polysaccharides show antimetastatic and immunomodulatory effects (Cao et al., 2014; Yue et al., 2015; Ben Mansour et al., 2017), while proteins and peptides bring cytotoxicity to the HepG2, A549 and pancreatic cancer cells (Ru et al., 2022; Wei et al., 2021; Qiao et al., 2021).

These varied bioactive compounds with different mechanisms of action make the sea cucumbers an attractive source in the quest to formulate novel anticancer therapeutics. The given research was therefore aimed at evaluating the therapeutic effectiveness of extract of sea cucumber *Holothuria atra* in a rat model with chemically-induced pituitary cancer, with special interest in what SCE can do with regard to tumor markers (CEA and CA19.9), pro-inflammatory cytokines (TNF-α and IL-1β), oxidative stress biomarkers (MDA, NO, SOD, GSH, CAT), and hormonal biomarkers (FSH, LH, PRL, E2 and insulin).

Materials and methods

Chemicals

Estradiol, which is used to create tumors, was purchased at Sigma-Aldrich (St. Louis, MO, USA).

Collection and Extraction of Bioactive Compounds

Biological activity compounds were obtained from the Cuvierian tubules of *Holothuria atra* that were sampled on the Egyptian coast of the Red Sea. Specimens were thoroughly washed using distilled water to remove sand, salt and debris and then cut up into small (2 cm × 2 cm) pieces using sterile instruments. The Cuvierian tubules were extracted, washed and kept in polyethylene bags. Using forceps the Cuvierian tubules were incised into tiny fragments and suspended in a 2% solution of acetic acid. The mixture was centrifuged at 14,000 rpm over 10 minutes

at 4 degrees Celsius, which gave a supernatant that was freeze dried and kept at minus 20 degrees Celsius awaiting further examination.

GC-MS Evaluation of Bioactive Components

Chemical profiling of the extract was carried out on a GC-MS system (Agilent 7890B GC plus 5977A MSD) housed at the Central Laboratories Network of the National Research Centre in Cairo. Separation was accomplished on a DB-5MS column (30 m × 0.25 mm, 0.25 μm film thickness). Helium served as the carrier gas with a flow velocity of 2.0 mL/min, and injection was splitless (1 μL). The oven began at 50°C (held 5 minutes), was raised gradually to 100°C at 5°C/min, and lastly to 320°C at 10°C/min, after which the temperature stayed at 320°C during 10 minutes. Detector and injector were maintained at 320°C and 280°C respectively. At 70 eV a scan range of m/z 25–700 was used and the solvent delay was 7 minutes to get mass spectra. Fragmentation patterns were then checked against the Wiley spectral libraries and NIST so that the compounds could be identified.

Experimental design

Animals

The National Research Centre located in Cairo, Egypt supplied thirty-two adult male Wistar albino rats aged 8–9 weeks and weighing 150–180 g. Rats were kept in polypropylene cages (eight rats per cage) with one week to become acclimated to laboratory conditions. They were kept at a constant temperature (25–28°C) and humidity (40–60%), and the 12 hours light/dark period. Rodent pellets and tap water were available without restriction. All the experimental work was carried out in accordance with the institutional regulations of the treatment and use of laboratory animals and was approved by the Ethics Committee of Faculty of Science, Al-Azhar University, Assiut.

Induction of Pituitary cancer

Estradiol (5 mg/kg 2 weeks) was subcutaneously injected in the adult female albino rats within a period of 13 weeks.

Experimental Groups

After induction of pituitary cancer, random assignment of the rats to four trial groups (n = 8 each) was done:

1- Control group: Healthy rats which were not subjected to treatment.
2- SCE group: Healthy rats received sea cucumber extract (SCE) intraperitoneally at 10 mg/kg/day over six weeks.
3- Estradiol group: Rats with Estradiol-induced pituitary cancer that received no further treatment.
4- Estradiol-SCE group: The rats had Estradiol induced colorectal cancer and were treated with SCE (10 mg/kg/day i.p.) over six weeks.

Collection of Blood Samples

After the administered therapy period was over, the rats had been weighed, and then they were fasted for the night. Anesthesia was administered (sodium pentobarbital 9.1 mg/kg diluted in sterile 0.9% NaCl through IM injection) and blood samples were then taken out of the retro-orbital plexus into heparinized and sterile glass capillaries. Cool centrifugation of whole blood samples at 100 RCF over 10 minutes was followed by isolation, aliquoting and storage of the sera at −80 °C until the tumor marker and pro-inflammatory cytokine analyses were carried out.

Hormonal profile

The hormonal profile (FSH, LH, PRL, E2 and insulin) was measured by reagent ELISA-kits of rats (purchased from Sunlong Biotech Co, Hang Zhou, China).

Oxidative and antioxidant determinations

To quantify the concentrations of glutathione (GSH), malondialdehyde (MDA) and nitric oxide (NO), along with catalase (CAT) and superoxide dismutase

(SOD) activity, ELISA kits of Sunlong Biotech Co., Hangzhou, China were used. These were read using a Dynatech Microplate Reader (Model MR 5000).

Tumor markers and immune-cytokines

ELISA kits of rat-specific serum (Sunlong Biotech Co., Hangzhou, China) were used to measure the serum CEA, CA19.9, tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) levels. Absorbance readings were taken with a Dynatech Microplate Reader (Model MR 5000).

Statistical analysis

Differences among the groups were compared by statistical analysis, one-way analysis of variance (ANOVA). Several comparisons were done with the help of Tukey post hoc test. It was found that a p-value of 0.05 or below was significant. All the analyses were conducted using SAS package (Version 1998; SAS Institute Inc., Cary, NC, USA), in accordance with standard statistical procedures.

Results

GC–MS analysis

In the sea cucumber extract, a number of chemical compounds, as determined by GC-MS, were found. There were five major parts that had identifiable molecular weights, relative abundances and retention times. Oleic acid, eicosyl ester was the most dominant compound that constituted 0.84% of all the peaks. Some of the other substances which were detected were Ethyl iso-allocholate, 9-Octadecenoic acid (Z)-, tetradecyl ester, 9-5-Chloro-6beta-nitro-5alpha-cholestan 3-one and 3,5,9-Trioxa-5-phosphaheptacos-18-en-1-aminiu. The compounds identified are mostly long-chain fatty acid esters indicating that the extract has bioactive compounds that have potential medicinal effects. All the details are shown in Figure 1 and Table 1 presents analytical data.

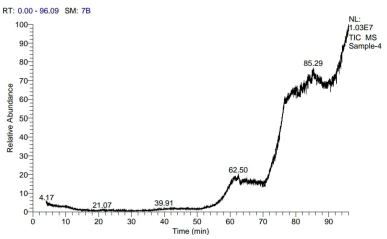

Figure 1. **Chromatogram of the extract of sea cucumber using GC-MS**

Table 1. Compounds that were identified in the sea cucumber extract through GC-MS

RT	Compound name	Molecular Formula	MW (g/mol)	Peak Area %
4.17	Ethyl iso-allocholate	$C_{26}H_{44}O_5$	436	0.70
21.07	9-Octadecenoic acid (Z)-, tetradecyl ester	$C_{32}H_{62}O_2$	478	0.70
39.91	Oleic acid, eicosyl ester	$C_{38}H_{74}O_2$	562	0.84
62.50	5-Chloro-6beta-nitro-5alpha-	$C_{27}H_{44}ClNO_3$	465	0.64

	cholestan 3-one			
85.29	3,5,9-Trioxa-5-phosphaheptacos-18-en-1-aminiu	$C_{44}H_{84}NO_8P$	785	0.76

Biomarkers and immune-cytokines:

Serum analysis showed a considerable increase in the CEA, TNF-α and IL-1β levels within the group with pituitary cancer relative to controls. Interestingly, SCE treatment of the pituitary tumor animals cut these biomarkers markedly and brought them back to a range close to that of the control sample (Figure 2).

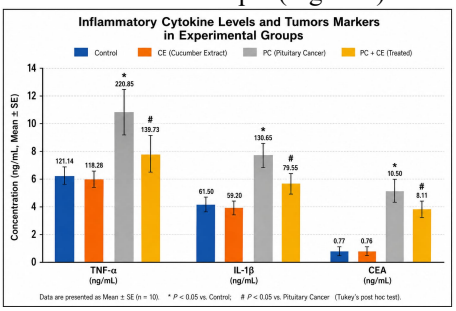

Figure 2: IL-1β, TNF-α and CEA levels in control, pituitary cancer and SCE-treated rats. The values are displayed as mean ± SE. ANOVA with one way was used to compare the groups, followed by Tukey's test for post-hoc comparison ($p < 0.05$).

Oxidative and antioxidant status:

Oxidative stress markers in serum exhibited significant disruptions in cancer-induced rats, with decreased antioxidant levels (GSH, SOD and CAT) and increased oxidative markers (MDA, NO). Encouragingly, SCE treatment significantly improved antioxidant status by elevating GSH, CAT, and SOD activities, while reducing MDA and NO levels (Figure 3).

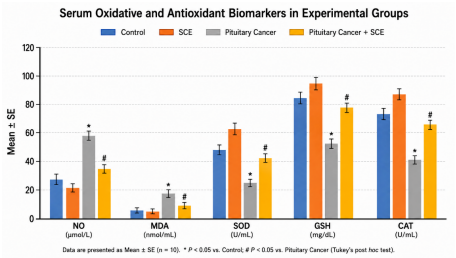

Figure 3: Serum oxidative and antioxidant biomarkers in control, cancer-induced, and SCE-treated rats. The values are displayed as mean ± SE. ANOVA was one-way to check the difference between groups, and post-hoc Tukey was done ($p < 0.05$).

Hormonal assay

The in vivo evidence revealed a significant insulin level drop and significant increase in the FSH, LH, TSH and E2 levels in the pituitary cancer group induced by Estradiol as compared with the control group. Compared to rats with pituitary cancer, SCE therapy was found to raise insulin and reduce FSH, LH, TSH and E2 levels significantly, thus, raising the hormonal assay levels towards normal values; (Figure 4).

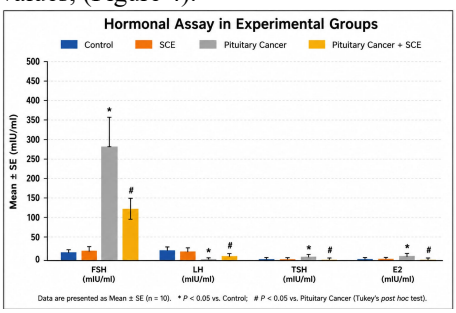

Figure 4. Mean values of hormonal assay in the control, cancer induced and SCE-treated rats. The values are displayed as mean ± SE. ANOVA (one-way) was applied to view group differences with post-hoc ($p < 0.05$) by Tukey.

Discussion

A rat pituitary tumor which had been experimentally induced by estrogen was considered to be a PRL producing tumor as light and electron microscopic observations and hormonal assay by Furth and Clifton (9) indicated. This paper evaluates the therapeutic promise of a new treatment of

pituitary cancer with sea cucumber extract (SCE) in hopes of increased efficacy and less side effects.

The cancer in the pitutary caused by Estradiol is associated with an increase in TNF-α and IL-1β that further stimulate inflammation and tumor development. Past studies (Kandeel et al., 2025) also discovered higher levels of the pro-inflammatory cytokines TNF-α and IL-1β in cancerous rats of the pituitary. Of the above-discussed pathogenetic mechanisms and markers, same research proposes that Estradiol stimulation of pituitary carcinoma is likely to have serious effects in disease environments that have a chronic inflammatory constituent (85). Chronic inflammation has also been reported to have a self-perpetuating nature and it changes the microenvironment due to aberrantly active transcription factors. Finally, growth factor, chemokine, cytokine and reactive oxygen species (ROS) balance changes take place in the cellular environment itself which subsequently supply the growth and survival axis necessary to de novo develop cancer and metastasis. The findings of a recently published study have many implications in a variety of pathologies in which NF-kB and HIF-1 have become de-regulated, such as rheumatoid arthritis and cancer (85). As a result, it is believed that grasping the cross talk between these two important transcription factors, NF-κB and HIF, will markedly advance the drug development process (85). Similar to pro-inflammatory cytokines, tumor marker (CA19.9 and CEA) levels are significantly elevated in Estradiol-induced pituitary cancer. Reactive oxygen species (ROS) are also the source of oxidative stress, an important factor in carcinogenesis, in the Estradiol induced pituitary cancer. Numerous signaling pathways that are essential for carcinogenesis are activated by ROS. For example, RhoA GTPase and nuclear factor-κB (NF-κB) are activated by hydrogen peroxide, which phosphorylates RhoA and activates IKKβ, which encourages carcinogenesis (Kim et al., 2017). Furthermore, ROS-induced PI3K/Akt pathway activation promotes metastasis and cell adhesion (O'Leary et al., 2012). Sanganna and Kulkarni (2013) indicated that all these ROS interfere with the functions of the important antioxidant enzymes like glutathione (GSH), glutathione peroxidase (GPx) and catalase (CAT), vital in eliminating free radicals. This disbalance enhances lipid peroxidation, dysfunction of proteins, and damage of DNA, which promote carcinogenesis. Finally, raised blood CEA and CA 19-9 levels are effective in detecting adenomas and pituitary carcinoma however are not very effective at forecasting the histopathological sizes and specific stages of the pituitary carcinoma.

TNF-α is a pro-inflammatory cytokine that plays a role in most stages of cancer evolution, such as inflammation, tumor growth and metastasis (Cruceriu et al., 2020). The fact that it is a contributor to tumorigenesis and how complicated its role in the tumor microenvironment is highlights its possible involvement as a therapeutic target and as a difficulty in obtaining effective treatment (Khan et al., 2025). Similar to TNF-α, IL-1β bestows growth on cancer cells as well as possessing certain anti-inflammatory effects (Mauer et al., 2015).

The current paper demonstrates that, when SCE is used in pituitary carcinoma model rats, it lowers concentrations of CEA and CA 19.9, as well as immune-inflammatory indicators (TNF-α and IL-1β), when compared with the control group. Various studies of natural extracts have shown that they can modulate inflammatory cytokines in cancer models. In a pituitary carcinoma model induced by Estradiol, the extract of SCE also showed a suppressive effect on these cytokines and tumor markers, indicating its importance in reducing inflammation and bolstering anti-tumor mechanisms. The medicinal potential of marine-derived bioactive compounds was highlighted by Alburae and Mohammed (2020) discovery that extracts from the marine extract demonstrated strong cytotoxicity against a range of cancer cell lines. These findings support our results by

indicating that the SCE might exhibit anti-inflammatory and anti-cancer characteristics by lowering TNF-α and IL-1β levels along with tumor markers (CEA and CA 19.9).

The current study demonstrated oxidative stress response by elevated levels of MDA and NO, alongside reduced levels of GSH and lower activity. Our outcomes show that rats with pituitary carcinoma had significantly higher MDA and NO levels, which is consistent with earlier studies showing that oxidative stress and inflammatory reactions are important factors in developing tumors (Kandeel et al., 2025). The excess androgens [43] stimulate excessive secretion of LH and FSH by the pituitary gland, and encourage weight gain, anovulation, the development of ovarian cysts and the production of ovarian androgen, either directly or through an insulin-mediated process of action [44, 45]. It was also found that insulin suppresses the activity of AMP activated protein kinase (AMPK) or adenosine monophosphate-activated protein kinase [46]. Low AMPK activation [47] and high cholesterol [48] encourage the manufacture of fatty acids, that is, lipogenesis. We have found that SCE therapy led to the decline of MDA and NO concentrations in cancerous rats and did promote the reestablishment of antioxidant capabilities like SOD, GPx, CAT, and GSH, supposedly because of its ability to deter or stabilize free radicals through its medicinal components. Extracts of marine SCE have already been reported to be abundant in bioactive peptides, with a diverse range of pharmacological properties, such as cytotoxic and anticancer activity (Aminin et al., 2015; Kalinin et al., 2008; Zou et al., 2005).

Conclusion

Finally, pituitary carcinoma induced by estradiol in vivo responded to sea cucumber extract with a considerable chemotherapeutic efficacy, and minimal adverse impact and toxicity. By efficiently regulating oxidative stress, inflammation, and immune responses, the extract helped to slow the growth of tumors. These results not only validate SCE therapeutic potential as a naturally occurring marine-derived agent, but they also raise the possibility that it could be used in clinical settings for the prevention and treatment of pituitary carcinoma. To confirm its safety and effectiveness in human populations, more research, including clinical trials, is necessary.

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