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A Comparative Analysis of Arm Regeneration in *Astropecten indicus* and *Ophiocnemis marmorata*

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Abstract

Echinoderms are renowned for their exceptional regenerative abilities, but interspecies comparisons have lacked rigorous quantitative analysis. This study compares arm regeneration in Astropecten indicus and Ophiocnemis marmorata under controlled conditions (37±0.7 ppt salinity, 17±0.3°C). Following 1 cm arm amputations (n=10/species), O. marmorata formed blastemas in 48–72 h, significantly faster than A. indicus (72–120 h, P<0.01). By week 5, 90% of O. marmorata had regrown arms to 2.0±0.2 cm, while only 55% of A. indicus achieved 1.8–2.0±0.3 cm by week 6. O. marmorata developed tube feet by week 2, compared to week 3 in A. indicus, and regained full mobility by week 4, while A. indicus required 5–6 weeks. Scarring was minimal in O. marmorata (<5%), compared to 15% in A. indicus. The survival rate of O. marmorata was higher (80%) compared to A. indicus (60%). These findings reveal distinct regenerative strategies: O. marmorata regenerates rapidly and without scarring, while A. indicus shows slower, fibrotic healing. The superior performance of O. marmorata, including faster blastema formation and complete anatomical restoration, makes it an ideal model for anti-fibrotic research, stem cell studies, and scaffold-free tissue engineering. This study provides the first quantitative framework for comparing echinoderm regeneration, offering promising insights into potential applications for human regenerative medicine.

***Keywords**: Echinoderm Regeneration, Scarless Healing, Blastema, Tissue Repair*

Introduction

Regeneration is the biological process by which organisms repair or replace damaged tissues, organs or limbs; this process varies significantly across the species. Invertebrates like planarians and hydra can regenerate their entire bodies from fragments, while echinoderms, such as starfish and brittle stars, excel at regenerating complex structures, including arms and internal organs. In contrast, mammals, including humans, exhibit limited regenerative capabilities, such as wound healing or liver regeneration, revealing a significant gap in regenerative potential (Elchaninov *et al.*, 2021).

Understanding the cellular and molecular mechanisms of regeneration is essential for regenerative medicine; this rapidly advancing field focuses on developing therapies aimed at restoring tissue function and treating conditions like chronic wounds, organ failure, and neurodegenerative disorders (El Miedany, 2022). The global regenerative medicine market, valued at USD 32.1 billion in 2023, and is projected to reach USD 398.77 billion by 2032, reflecting a compound annual growth rate of 32.4% from 2024 to 2032 (Allied Market Research, 2023).

A major focus of regenerative medicine is the study of conserved signaling pathways that regulate regeneration. Bone morphogenetic proteins (BMP), transforming growth factor beta (TGF-β), and Wnt pathways play key roles in cell proliferation, differentiation, and tissue remodeling, across various species (Zou *et al.*, 2021). In echinoderms, BMP and TGF-β pathways drive blastema formation and tissue patterning, enabling rapid and precise regeneration of lost structures (Xiao *et al.*, 2021). Understanding these pathways is essential for developing novel therapies that can enhance human tissue repair, including stem cell-based treatments and tissue

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engineering approaches (Mosaddad *et al.*, 2024). Echinoderms, in particular, provide valuable insights due to their remarkable regenerative abilities, which are significantly greater than those of mammals (Carnevali *et al.*, 2024).

Echinoderms, such as starfish, brittle stars, sea urchins, and sea cucumbers, are exceptional models for regeneration research. Their ability to regenerate arms, spines, and organs with high fidelity relies on cellular dedifferentiation, proliferation, and redifferentiation, all regulated by BMP and TGF-β signaling (Sader and Roy, 2022). These regenerative abilities are crucial for survival in marine environments where physical damage from predation, wave action, or environmental stressors is common (Yao *et al.*, 2024). Despite extensive studies on species like *A. rubens* (starfish) and *A. filiformis* (brittle star) have been extensively studied, other echinoderms, such as *A. indicus* (starfish) and *O. marmorata* (brittle star), remain under-explored, despite their remarkable regenerative potential (Carnevali *et al.*, 2024). Limited studies on these species make them promising yet underutilized models for understanding regeneration mechanisms (Xiao *et al.*, 2021).

The ecological and evolutionary significance of echinoderm regeneration suggests that these abilities may enhance survival in dynamic marine environments, where physical damage from predation or environmental factors is common (Yao *et al.*, 2024). Echinoderms relatively simple anatomy and accessibility make them a practical and cost-effective choice for experimental studies, complementing more complex vertebrate models like zebrafish or mice (Carnevali *et al.*, 2024). Advances in high-resolution imaging and quantitative analysis have further enhanced the study of echinoderm regeneration, enabling detailed tracking of morphological and temporal dynamics during tissue regeneration. These technological improvements have revealed the intricate cellular reprogramming and signaling events involved in regeneration, offering insights into evolutionary adaptations that enable precise tissue repair (Sader and Roy, 2022).

This study represents a novel comparative analysis of arm regeneration in *A. indicus* and *O. marmorata*, two understudied echinoderm species with significant regenerative potential. Unlike prior research that focused on well-characterized models like *A. rubens*, this work employs a streamlined methodology involving standardized arm amputation, high-resolution imaging, and quantitative analysis to document the regeneration process over 4–6 weeks (Czarkwiani*et al.,* 2021). By capturing the morphological progression of arm regrowth, including the regeneration of spines, tube feet, and nerve cords, this study establishes these species as viable models for regenerative biology. The findings contribute to our understanding of echinoderm regeneration and have implications for regenerative medicine, particularly in developing strategies for human tissue repair, such as enhanced wound healing and tissue engineering (Mosaddad *et al.*, 2024). By leveraging the unique regenerative capabilities of *A. indicus* and *O. marmorata*, this research bridges marine biology and medical science, laying the groundwork for future investigations into the genetic and cellular basis of regeneration and its clinical applications.

Materials and Methods

Study area and specimen collection

Live specimens of *A. indicus* (common starfish) and *O. marmorata* (brittle starfish) were collected from Mudasalodai fish landing center (N 11°29'25.548", E 79°45'38.6172") as by catch by local fishermen using trash nets between April and March 2024 (Figure 1 A-B). These specimens were obtained alive from the by catch of local fishermen using trash nets, which provided a continuous supply of starfish species for the study. Figure 1-C Close-up view of a live *Astropecten indicus* specimen, showing its characteristic arm structure and morphology. Figure 1-D Close-up view of a live *Ophiocnemis marmorata* specimen, highlighting its distinc arm shape and disk structure.

This biodiversity-rich region provided a reliable supply of the target species. A total of 10 specimens per species, all free from visible physical infection were selected. The specimens were transported in seawater-filled bags to minimize stress and acclimated in temperature-controlled tanks for six hours. Species identification was confirmed using the FAO identification sheet (NRC Guide, 2010).

Ethics declaration

This study followed ethical guidelines for research involving marine organism. Both species examined are classified as non-endangered according to the IUCN Red List. The research protocol received approval from the Institutional Animal Ethics Committee of Aarupadai Veedu Medical College and Hospital (IAEC No: AVMC/IAEC/2024/10/28/01).

Experimental setup and animal monitoring

Ten specimens of Adult *A. indicus* (arm span 4–8 cm) and *O. marmorata* (disc diameter 4–8 cm) were housed in 500 L glass aquaria filled with artificial seawater (salinity 37±1 ppt, temperature 17±0.5°C, pH 7.8–8.2), the artificial seawater was prepared using a commercial marine salt mix (Instant Ocean, Spectrum Brands). A 4 mm layer of fine silica sand was added to mimic natural benthic substrates.

Each aquarium was equipped with a recirculation filtration system, a protein skimmer, and maintained a 12:12 h light: dark cycle (50 µmol photons $m^{-2}s^{-1}$) to ensure water quality and photoperiod stability. The specimens were acclimatized for two weeks prior to the start of experiments to quarantine physiological stability. Representative images of the specimens are shown in Figure 1C–D, Weekly water changes of 10% using pre-mixed artificial seawater helped maintain consistent water quality (Wahltinez *et al.*, 2023).

Feeding and behavioral observations

Specimens were fed twice a week with 1 cm^3 portions of cuttlefish (*Sepia officinalis*) and live mussels (*Mytilus edulis*), which were placed directly on the substrate to mimic natural foraging (Calderwood *et al.*, 2015). Daily behavioral assessments were conducted, categorized activity as either normal (*e.g.*, active feeding, arm movement) or abnormal (*e.g.*, arm twisting, ulceration). Any specimens exhibiting abnormal specimens were transferred to 50 L isolation tanks with identical conditions for close monitoring, following standard echinoderm care protocols. Behavioral data were recorded in a logbook for subsequent analysis.

Induction of regeneration

Regeneration was induced by amputating 1 cm from the distal third of one arm of each specimen using a sterile razor blade (Figure 2), following established protocols. Non-amputated controls were excluded, from the study, as the goal was to specifically compare regenerative responses of *A. indicus* and *O. marmorata* under controlled conditions. Both species were maintained in identical environmental conditions (salinity of 37±0.7 ppt and temperature of, 17±0.3°C) to ensure uniform regeneration environments. To minimize stress, specimens were anesthetized for 5 minutes in a solution of 3.5% magnesium chloride hexahydrate ($MgCl_2$ $6H_2O$) mixed 1:1 with artificial seawater (37 ppt) (Wilkie and Carnevali *et al.*, 2024). After amputation, specimens were returned to their primary aquaria and monitored daily for signs of recovery or complications using standardized criteria: (1) wound closure, and (2) blastema formation timing as measured by calibrated imaging protocols. The regeneration process was observed over a period of 4-6 weeks, consistent with the typical timelines for echinoderm regeneration. (Dai *et al.,* 2016, Afshar *et al.,* 2023).

Figure 1. Illustrates the collection process of the live specimens of *Astropecten indicus* and *Ophiocnemis marmorata* from the Mudasalodai fish landing center, followed by their transport for analysis

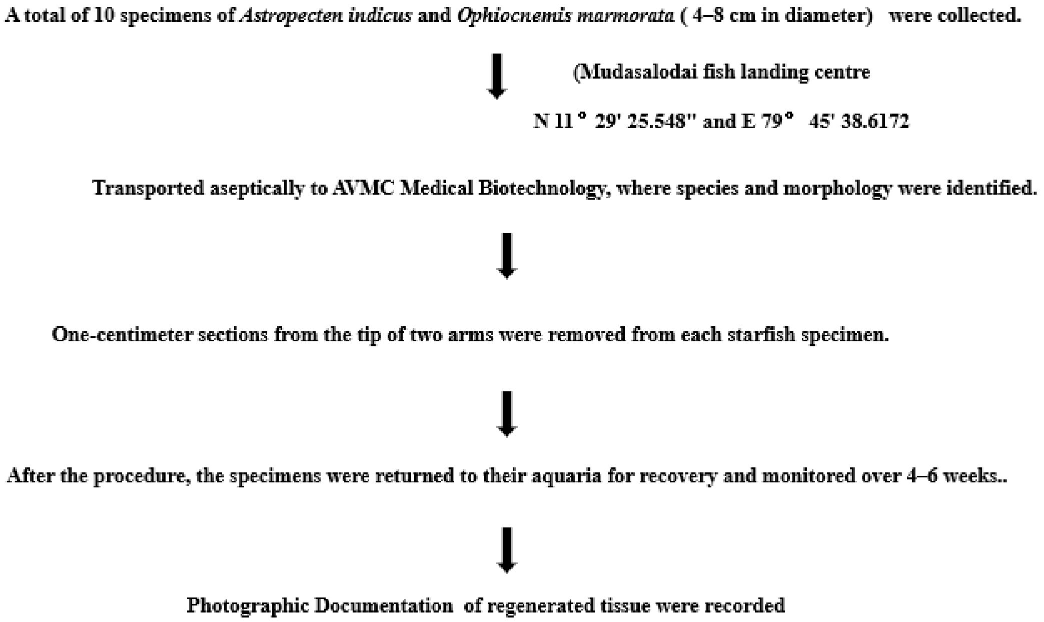

Figure 2. Flowchart of the Experimental Process for Inducing Arm Regeneration and Monitoring Progress in *Astropecten indicus* and *Ophiocnemis marmorata*

Photographic documentation

High-resolution images were captured weekly to document arm regeneration in *A. indicus* and *O. marmorata* over a 4 to 6 weeks' period following amputation. A Nikon D850 camera (45.7 MP, 105 mm macro lens) was mounted on a tripod 30 cm above the aquarium, with consistent lighting (100 µmol photons $m^{-2}s^{-1}$, LED source) to ensure clarity in the images. The photographs recorded morphological changes, including blastema formation, spine regrowth, tube feet development, and nerve cord regeneration. Baseline images (pre-amputation) were taken for each specimen to serve as a reference. Regeneration rates were assessed by visually comparing weekly images to measure the increase in arm length increase, using a calibrated scale bar embedded in each image (Alarcon, 2015). Species-specific differences were observed, such as faster arm regrowth in *O marmorata* compared to *A. indicus*, noted through visual inspection. The images were stored in RAW format and processed using Adobe Photoshop (version 23.0) for brightness and contrast adjustments to enhance visibility of the regenerated structures (Franco, 2011).

Data analysis

Statistical of comparisons of regeneration length, survival rate, and blastema formation timing between species were performed using Student's t-test. Data are expressed as mean ± SD, and a $P< 0.05$ less than was considered statistically significant.

Results and Discussion

Environmental stability and specimen health

Ten specimens each of *A. indicus* (arm span: 4–8 cm) and *O. marmorata* (disc diameter: 4–8 cm) were maintained in six 500L aquaria for six weeks under controlled conditions: (salinity of 37±0.7 ppt, temperature of 17±0.3°C, and pH of 7.9±0.15). Stable water quality was maintained by performing weekly 10% water changes and using a recirculation filtration system. The survival rates were 60% for *A. indicus* (6 out of 10, with one death due to ulceration) and 80% for *O. marmorata* (8 out of 10). The study carefully observed abnormal behaviors, including arm curling and reduced feeding, in four *A. indicus* and two *O. marmorata* specimens; these individuals were isolated in 50L tanks, and when they showed no further complications. Specimens were fed twice-weekly 1g portions of cuttlefish (*Sepia officinalis*) and mussels (*Mytilus edulis*) to promote normal foraging behavior.

Regeneration rates

On August 11, 2024 1 cm was amputated from the two arms of ten specimens from each species. Regeneration was measured on one arm per specimen using a 1 mm scale (see Fig. 3A-B). Initial signs of tissue regeneration, such as blastema formation, were first mildly observed around the 5th week, although only endpoint measurements (final regrowth after 6 weeks) were recorded. In *O. marmorata*, 90% of the specimens exhibited complete arm regrowth by the 5th week (between approximately August 27 to September 10). The mean regrowth was measured at (2.0±0.2 cm). By the end of the 6th week (around September 22), 100% of the specimens had achieved complete regeneration of their amputated arms, which also measured (2.0±0.2 cm). The rapid regeneration observed in *O. marmorata* within 5 weeks indicates highly efficient cellular mechanisms that facilitate scarless wound healing with minimal fibrosis. This efficiency may be attributed to effective blastema formation and tissue regeneration, resulting in little scarring.

In contrast, only 55% of specimens of *A. indicus*, reached complete arm regeneration by the 6th week (between 30-42 d, September 10th to September 22nd. The mean regrowth was 1.9 cm, with a range of 1.8-2.0±0.3 cm and functional tube feet were present as detailed in Table 1. The difference in regeneration speed was statistically significant ($P < 0.01$), confirming that *O. marmorata* regenerated more rapidly than *A. indicus*. The slower, more structured regeneration process observed in *A. indicus* over 6 weeks indicates a gradual tissue remodeling process, likely involving increased fibrosis and a slower regeneration rate compared to *O. marmorata*. This slower process may be the advantageous for the scaffold-based tissue engineering, where precise and structured tissue growth is essential. Table 1 presents weekly regrowth and full regeneration percentages for *Ophiocnemis marmorata* and *Astropecten indicus*. The rapid regrowth observed in *O. marmorata* is a significant finding, emphasizing its potential for scarless wound healing. In contrast, the slower regrowth seen in A. *indicus*, provides valuable insights into the gradual process of tissue remodeling, which may particularly relevant for tissue engineering applications. The standard deviations, calculated from single measurements taken from each arm across of ten specimens per species, reflect the variability of the data and indicate the reliability of the measurements.

Morphological changes

Photographic documentation revealed distinct patterns of regeneration (Figure 3A-B). In *A. indicus,* a blastema formed 72 to 120 h (3–5 d) after amputation, initially appearing as a transparent, conical bud at the site of injury. By week 2, rudimentary spines began to emerge, followed by the development of non-functional tube feet by week 3. By week 4, the radial nerve cord and skeletal ossicles became visible, with functional arm movement such as the ability to grip. substrates, was restored in 40% of specimens by week 5 and in 70% of specimens by week 6. Minor fibrotic scarring was observed in 15% of specimens, localized at the amputation site; however, this didn't significantly impair regeneration or overall function.

In contrast, *O. marmorata*, demonstrated a faster regeneration process. The blastema formed within 48 to 72 h (2 to 3 d) after amputation. By the end of the first week, their spines began to appear, and by the second week, functional tube feet developed. The radial nerve cord regenerated by the third week, and the complete arm exhibited flexibility was restored by the fourth week. Scarring was minimal affecting less than 5% of the specimens, and the regrowth was uniform, indicating efficient wound healing. These observations underline the more rapid and effective morphological development of *O. marmorata* comparison to *A. indicus.*

This study provides insights into the regenerative mechanisms of *O. marmorata* and *A. indicus*, providing a comparative analysis of their regeneration strategies within the Echinodermata phylum. Notably, *O. marmorata* exhibits faster regeneration, completing arm regrowth in 16 to 30 d, compared to 30 to 42 d for *A. indicus*. This key

Table 1. Weekly Regrowth Data and Full Regeneration Percentages for *Ophiocnemis marmorata* and *Astropecten indicus*

Species	Time Point	Specimens Measured	Fully Regrown Specimens	Mean Regrowth (cm)	Standard Deviation (cm)	% Fully Regrown	Regeneration Rate (cm.week^{-1})
Ophiocnemis marmorata	Week 5	10	9	2.0	± 0.2	90% (16–30 d)	0.133
Ophiocnemis marmorata	Week 6	10	10	2.0	± 0.2	100% (16–30 d)	0.133
Astropecten indicus	Week 5	10	~5 (estimated)	~1.4 cm	± 0.3	~50% (30–42 d)	~0.28
Astropecten indicus	Week 6	10	5	1.9	± 0.3	55% (30–42 d)	0.06

difference reflects their evolutionary adaptations to their respective habitat and ecological roles. *O. marmorata* regenerates arms via epimorphic regeneration, driven by coelomic epithelial cells, with blastema formation occurring within 48 to 72 h (Khadra *et al.*, 2018). In contrast, the regenerative process of *A. indicus* exhibits a more complete regeneration process, involving a combination of wound-based blastema regeneration (WBR) and morphallaxis.

The variation in regeneration speed among species correlates with tissue complexity, with simpler organisms typically regenerating more quickly than more complex ones. *O. marmorata* forms a blastema early, within 48 to 72 h (2–3 d), a rapid process driven by the proliferation of coelomic epithelial cells. This aligns with faster regeneration observed in species like *Amphiura filiformis* and *Ophioderma longicaudum* (Khadra *et al.*, 2018). In contrast, *A. indicus* exhibits delayed blastema formation occurring between 72 to 120 h, requiring more extensive tissue reorganization and exhibiting fibrosis in 15% of specimens (Ferreiro *et al.*, 2018). Similarly, *Luidia maculata* which takes 5 to 7 weeks, and relies on cell division and tissue reorganization (Medina-Feliciano *et al.*, 2021). This difference can be attributed to the thicker and less flexible arms of *A. indicus*, which require more substantial remodeling.

When comparing regeneration times, *A. indicus* regenerates faster than *Echinaster sepositus* completing arm regeneration in 4 to 6 weeks, compared to 6 to 8 weeks for *E. sepositus*, which exhibits delayed skeletogenesis (Khadra *et al.*, 2015). Similarly, *Asterina gibbosa* regenerates its arms in 5 to 7 weeks, whereas *Astropecten verruculosis* takes 6 to 8 weeks, reflecting differences in tissue

i) *Astropecten indicus*

ii) On August 11, 2024, two arms of the starfish *Astropecten indicus* were carefully dissected to investigate their regenerative properties

iii) Within a few weeks, the dissected arms showed signs of regeneration, triggering cellular proliferation and tissue reformation as part of the starfish's natural regenerative process.

i) ***Ophiocnemis marmorata***

ii) On August 11, 2024, two arms of the brittle star *Ophiocnemis marmorata* were dissected to study their regenerative capacity

ii) The amputated arm fully regenerated within a few weeks, stimulating cellular proliferation and tissue regeneration, which was closely monitored to understand the underlying mechanisms of starfish arm reformation

Figure 3. Arm Regeneration Study in *Astropecten indicus* and *Ophiocnemis marmorata*

complexity (Garcia-Arrarás and Valentin-Tirado, 2011). However, *A. indicus* regeneration time aligns with that of *Patiria miniata*, *Arcaster typicus* and *Linkia laevigata*, all of which regenerate in 4 to 6 weeks (Hotchkiss, 2009; Meyer and Hinman, 2022). These findings suggest that ecological factors such as habitat and environmental stressors may influence the rate and efficiency of regeneration. While faster regeneration may provide a survival advantage in certain environments, species with more complex structures *e.g.*, *A. indicus* may require more extensive tissue remodeling affecting regeneration speed.

Fibrosis also varies across species, while *O. marmorata* exhibiting minimal fibrosis, similar to species like *Asterina gibbosa* which shows low fibrosis (Khadra *et al.*, 2015; Medina-Feliciano *et al.*, 2021; García-Arrarás and Valentin-Tirado, 2021). In contrast *A. indicus* shows fibrotic patches and collagen deposition, similar to *Asteria rubens* Hernroth *et al.*, 2010). Other species, such as *E. sepositus* and *L. maculata,* show moderate fibrosis*,* but less than *A. indicus*. While species like *Holothuria glaberrima* and *A. typicus* also exhibit low fibrosis (San Miguel-Ruiz and García-Arrarás, 2007). While *Linckia laevigata*, displays minimal fibrosis, shows enhanced regenerative efficiency (Chen, 2019). Despite the collagen deposition in *A. indicus*, the matrix remodeling in echinoderm is more advanced than mammalian wound healing (Ferrario *et al.*, 2018).

Regarding blastema formation, adult *Patiria miniata* exhibits a blastema timing similar to *A. indicus*, although WNT and Sox2 pathways were not detected in photographic methods (Cary *et al.*, 2019). Mean while *L. laevigata* shows blastema formation between 72 to 96 h, driven by BMP signaling, much like *O. marmorata*. In comparison, Planarian neoblasts and salamander dedifferentiated cells accelerate blastema formation, contrasting with the action of echinoderms' resident stem cells in regeneration (Sandoval-Guzmán *et al.*, 2014; Reddien, 2018). Additionally, genes like SRAP and VASA in Echinoderm have been observed to regulate proliferation, particularly in *P. miniata* (Oulhen *et al.*, 2016).

In terms of tissue growth, O*. marmorata* regenerates muscle, skeletal, and neural structures quickly, resembling species like *Amphiura filiformis* and *Ophioderma longicaudum* (Alarcon, 2015; Khadra *et al.*, 2018). *A. indicus* regenerates ossicles, spine, tube feet, and nerve cords, similar to the regeneration observed in adult of *Patiria miniata*, *Archaster typicus*, and *Linckia laevigata* (Cary *et al.*, 2019; Chen, 2019). Notably, *A. indicus* regrows ossicles faster than *Echinaster sepositus*, while *Asterias rubens* exhibits slower skeletal growth due to fibrosis (Hernroth *et al.*, 2010; Khadra *et al.*, 2015; García-Arrarás and Valentin-Tirado, 2021).

Although this study did not include molecular assays, previous transcriptomic analyses in related species (*e.g.*, *Linckia laevigata*, *Patiria miniata*) have demonstrated that BMP/TGF-β signaling regulates blastema initiation, while WNT and Sox2 pathways govern dedifferentiation and tissue patterning (Cary *et al.*, 2019; Xiao *et al.*, 2021). Given the rapid, scarless regeneration observed in *O. marmorata*, it is plausible that similar molecular cascades are highly active. Conversely, the slower, fibrotic regeneration in *A. indicus* may reflect attenuated BMP/TGF-β activity or the upregulation of fibrosis-associated pathways. Future transcriptomic and proteomic profiling will be essential to clarify these distinct mechanistic differences.

Echinoderm-derived compounds, such as squalene and sterols, show promise in wound healing and cancer research. For instance, *A. typicus* extracts have been shown to promote scarless wound healing in zebrafish models (Dai *et al.*, 2016). These compounds, particularly sterols may induce apoptosis in cancer cells through reactive oxygen species (ROS) pathways. Future research using advanced techniques like GC-MS/MS, RNA sequencing, and CRISPR should further characterize these compounds and related regenerative pathways including WNT, BMP/TGF-β, SRAP, VASA in echinoderms and their potential applications in human regenerative medicine.

This study has several limitations, the sample size was relatively small (n= 10 per species), which may reduce statistical power and limit the generalizability of the findings. The absence of molecular assays restricted the ability to gain mechanistic insights into the regeneration process, and the lack of non-amputated control groups weakened the robustness of comparative analyses. Furthermore, inherent structural difference between species, such as the thicker arms of *A. indicus*, may influence regeneration rates, complicating direct cross- species comparisons. Future studies should incorporate larger sample sizes, include non-amputated controls, and employ transcriptomic or proteomic analyses to validate these observations. Comparative research across a wider range of echinoderms species, such as *A. typicus* and *L. laevigata would* further enhance our understanding of regenerative pathways and their biomedical relevance, particularly concerning stem cell signaling and scarless healing mechanisms. Future studies should also investigate the role of echinoderm-derived compounds in human regenerative therapies, particularly focusing on stem cell signaling pathways (ROS) pathways.

Conclusion

The regenerative abilities of *A. indicus* and *O. marmorata* provide valuable insights into tissue regeneration. Investigating the genetic and molecular processes involved in their restoration is crucial for enhancing our understanding of tissue repair mechanisms. These findings improve our knowledge of how various species regenerate and uncover new pathways that could lead to better medical alternatives. Such research establishes a foundation for future therapeutic developments that may offer solutions for human tissue injuries and wounds. Studying the regenerative process of these species is essential, as it help medical professionals create more effective treatments and drive significant advancements in regenerative medicine.

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