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Research advancement of *Apostichopus japonicus* from 2000 to 2021

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This study aims to establish a quantitative and qualitative evaluation model of sea cucumber *Apostichopus japonicus* research. Data from 2000 to 2021 were obtained from the Web of Science Core Collection (WoSCC) of Thomson Reuters. Bibliometrics and CiteSpace software were used to analyze authors, exporting countries, journals, influential articles, research areas, institutions, research hot spots, and trends. A total of 1,358 research papers on *A. japonicus* research were identified from 2000 to 2021. The number of papers published in this field is rapidly increasing, and the research phase can be divided into initial, developmental, and stabilization phases. Research on *A. japonicus* is mostly conducted in China, followed by Japan and the United States. Hongsheng Yang, Chenghua Li, and Shuanglin Dong are the lead authors. Research activities are focused on genetics and breeding, growth and development, immunology and disease, aestivation, regeneration, and food processing. Gut microbiota, activation, and collagen are potential research hot spots. The project highlights differences in the level of research between countries and teams, and regions with more developed industries or richer resources need further support. Governments or organizations are encouraged to 1) promote the development of the *A. japonicus* industry through the development or implementation of policies; 2) further participate in the research, production, and processing of *A. japonicus*; and 3) strengthen international exchange and cooperation to bring economic benefits to farmers in suitable breeding areas through technology sharing.

KEYWORDS

Apostichopus japonicus, co-citation analysis, research hot spots, frontier prediction, bibliometrics

Introduction

More than 1,500 species of sea cucumbers have been recorded in the world (Liao, 1997). Sea cucumber *Apostichopus japonicus* (Echinodermata, Holothuroidea) was first described and reported by Selenka (1867). Considering its richness in bioactive substances such as triterpene glycosides, polysaccharides, and neuropeptides, it has

been a valuable traditional food and nutraceutical, especially in East Asian countries (Bordbar et al., 2011; Ramírez-González et al., 2020). Only approximately 60 species have exploitation value, among which *A. japonicus* is the most economically important species (Kinch et al., 2008). In 2021, China's total production of *A. japonicus* will be 350 million pounds, about 1.6 billion pieces, and the value of the whole industry chain will be about \$9 billion (Sea Cucumber Industry Branch of China Fisheries Association, 2022). Wild *A. japonicus* is mainly found in the temperate waters of the western Pacific Ocean, including Japan, Korea, the Russian Far East, and Northeast China (Cui and Zhao, 2000). China is a major producer and consumer of *A. japonicus*. The economic growth and increased consumption of the Chinese society provide a good environment for the development of the *A. japonicus* industry (Ru et al., 2019). In addition to seabed seeding, three well-established aquaculture models, namely, shrimp pool coculture, floating raft culture, and bottom net culture, are being developed in China (Chang, 2002).

In the late 19th century, the Japanese scholar Kakichi Mitsukuri first studied the morphology and ecological habits of *A. japonicus* (Mitsukuri, 1897; Mitsukuri, 1905). The early research on *A. japonicus* was also conducted in Japan by a group of technical application talents who studied the growth and reproduction of *A. japonicus*. In 1938, Densaburo Inaba first tried to breed sea cucumbers in captivity (Midori and Kenichiro, 1981). In 1950, he worked with Takeshi Imai and Ryuhei Sato to develop the use of colorless flagellates as bait for sea cucumber larvae (Imai et al., 1950). Scholars Kinoshita and Tanaka reported on the short aestivation time of sea cucumbers from Hokkaido (Tanaka, 1958; Furukawa et al., 2016). A few years later, they sampled and analyzed the *A. japonicus* digestive tract and found that it mainly consisted of gravel, sediment, and shell fragments, providing a research basis for the culture of the species. Choe (1963) studied the genetics and regeneration of sea cucumbers. Over the next 60 years, Russia, South Korea, United States, and China will work together to improve *A. japonicus* breeding, disease control, and growth performance.

Zoology, agriculture, and other disciplines have begun using knowledge analysis and visualization tools, such as the CiteSpace software, to investigate and analyze water pollution (Hu et al., 2019; Liu et al., 2019), soil erosion (Liu et al., 2020; Huang X. et al., 2021), and marine conservation (Picone et al., 2021; Wang Z. Q. et al., 2021). In the case of *A. japonicus*, although we have a lot of basic research published in journals, access to cutting-edge data in the industry still relies on regular review articles, technical summits, and especially the support of government agencies in charge of fisheries. Scholars have not attempted to systematize and visualize the knowledge about *A. japonicus* developed from basic or industrial research. In the present study, we used bibliometrics and CiteSpace software to qualitatively or quantitatively analyze and visualize literature

from 2000 to 2021, estimate the global scientific outputs of *A. japonicus* research, and analyze the hot spots and trends, which aims to provide fundamental data for further research on *A. japonicus* and encourage governments and organizations to promote the development of the *A. japonicus* industry through the development or implementation of policies.

Data and methods

Data sources

The data retrieval process was completed on 1 April 2022. This study is based on the Web of Science Core Collection (WoSCC) database, including Science Citation Index Expanded, Social Sciences Citation Index, Current Chemical Reactions, and Index Chemicus. Both *A. japonicus* and *Stichopus japonicus* were used in research papers because of the different usage habits of scholars or other factors. Therefore, the terms “*Apostichopus japonicus*” and “*Stichopus japonicus*” were used as keywords to retrieve titles, author information, abstracts, and references from 2000 to 2021, respectively. On this basis, we used the Boolean Operator “OR” to combine the two search formulas and obtained 1,358 research papers on *A. japonicus*. The bibliographies of 1,358 papers were downloaded and exported as “plain text files,” and the records were set to “full records and cited references.” The three downloaded text files were imported into the CiteSpace analysis software to perform taxonomy and visual analysis of the research literature.

Research method

To present the research hot spot and development trend of this subject intuitively, objectively, quantitatively, and authentically, we used bibliometrics theory and CiteSpace 5.8.R3 as research tools. As proposed by Allen Pritchard in 1969, bibliometrics is defined as “the assembling and interpretation of statistics relating to books and periodicals ... to demonstrate historical movements, to determine the national or universal research use of books and journals, and to ascertain in many local situations the general use of books and journals” and is commonly used to analyze published literature and organize knowledge (Pritchard, 1969; Khalil and Crawford, 2015). CiteSpace is an excellent scientific mapping tool based on bibliometrics, and it was developed by Dr. Chaomei Chen, a tenured professor at Drexel University (Chen, 2006). It provides researchers with a powerful tool for the analysis of historical literature and creating a summary of the characteristics of the discipline through time-sharing and dynamic citation analysis visualization techniques (Chen et al., 2015). CiteSpace allows the identification of emerging trends while reducing our reliance on

domain experts or prior knowledge base. This approach makes the analysis repeatable with new data and can be validated by different analysts. The evolution of the research field can be shown centrally on citation network maps. Based on the citation nodes and co-citation clusters on the map, the research frontiers and hot spots in the field can be analyzed.

Results

Analysis of publication quantity

There is a positive correlation between the research heat and the number of articles published. Comparing the number of publications per year is an easy way to get an idea of how hot a particular research area is. Based on the search results, annual trends in *A. japonicus* research publications from 2000 to 2021 are presented, as shown in Figure 1. In this period, studies on *A. japonicus* have increased rapidly. We divided the development of *A. japonicus* research into three stages. Prior to 2009, the research was at a preliminary stage, in which fewer than 20 articles were published per year. The range of studies is relatively narrow. During this period, researchers focused primarily on growth performance and immune response, accounting for 20.22% and 24.72% of 93 papers, respectively. Common keywords include temperature, salinity, oxygen consumption, arginine kinase, and microsatellite. During the development period from 2009 to 2016, *A. japonicus* research rapidly became a research hot spot with an average annual growth rate of 22.91%. The research direction of this period has the characteristics of diversification and refinement. It has been in a stable phase since 2017, in which the number of *A. japonicus*-related publications exceeded 130. The rapid rise in the number of publications signifies that *A. japonicus* is becoming an increasingly important vector for scientific research.

Analysis of the research teams

Research teams led by high-yielding writers are the main force behind scientific work (Wuchty et al., 2007). The core team and highly productive group of authors for the *A. japonicus* study were therefore identified as being necessary. Table 1 lists the top 10 authors in the field of *A. japonicus*. According to Price's law of bibliometrics, which states that "On the same topic, half of all articles are written by highly effective authors" (Wei et al., 2020), we set N_{max} as the number of publications of the most productive authors and $(1, N_{max})$ is the total number of publications. The mathematical expression is as follows:

$$\frac{1}{2}(1, N_{max}) = x(m, N_{max}) = x(1, m) \quad (1)$$

where m is a positive integer set by Price, and the total number of articles published by author groups with publications greater than m is approximately half of all articles (Price et al., 1984). The formula can be derived by further calculation as follows:

$$m \approx 0.749 \times \sqrt{N_{max}} \quad (2)$$

The positive integer m is approximately 9 when $N_{max}=N_y$, $H_S=123$. In other words, authors who have published nine or more papers in the field of *A. japonicus* can be considered highly productive, with a total of 134 authors, or only 4.43% of the total number of authors. Therefore, a stable core group of authors has not been formed in the field of *A. japonicus* research, and the concentration of authors is low. Every year, a large number of talents are absorbed into the field of *A. japonicus*. As shown in Table 1, the authors in the field of *A. japonicus* are mainly distributed in the Institute of Oceanology, Chinese Academy of Sciences (IOCAS), Ningbo University (NBU), and Ocean University of China (OUC). Team Hongsheng Yang from

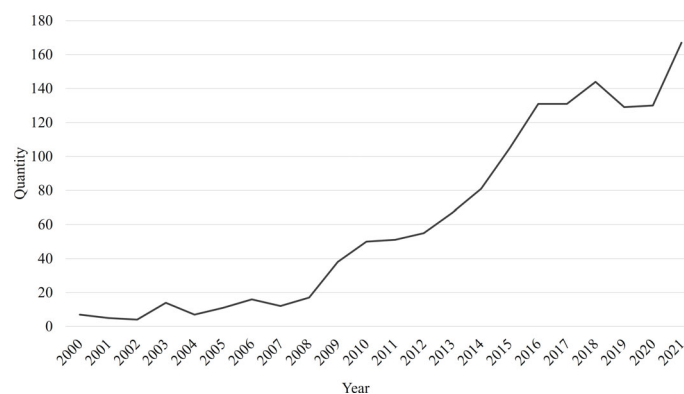


FIGURE 1
Trends of publications on *Apostichopus japonicus*-related research from 2000 to 2021.

TABLE 1 Top 10 authors in the field of *Apostichopus japonicus* from 2000 to 2021.

Ranking	Author	Count
1	Yang, Hongsheng (IOCAS)	123
2	Li, Chenghua (NBU)	113
3	Dong, Shuanglin (OUC)	86
4	Zhang, Weiwei (NBU)	82
5	Zhang, Libin (IOCAS)	80
6	Shao, Yina (NBU)	67
7	Liu, Shilin (IOCAS)	61
8	Chang, Yaqing (Dalian Ocean University)	59
9	Sun, Lina (IOCAS)	58
10	Gao, Qinfeng (OUC)	52

IOCAS, Institute of Oceanology, Chinese Academy of Sciences; NBU, Ningbo University; OUC, Ocean University of China.

IOCAS, Team Chenghua Li from NBU, and Team Shuanglin Dong from OUC are top teams in the field of *A. japonicus*. Identifying the central research team allows us then to have a timeline of the development of each research direction through its articles.

Analysis of source countries

The country-level analysis also deserves our consideration. The count of independent studies and the frequency of inter-country cooperation can reflect the status and problems of *A. japonicus* research. An analysis of the main source countries for the *A. japonicus* study is presented in Table 2. China contributed 1,026 articles, accounting for 75.55% of the total number of articles on *A. japonicus*, followed by Japan with 113 published articles (8.32%). Notably, Japan is not only a pioneer in research

TABLE 2 List of five main source countries of *Apostichopus japonicus* research papers from 2000 to 2021.

Ranking	Country	Count	Percentage
1	China	1,026	75.55%
2	Japan	113	8.32%
3	USA	74	5.45%
4	South Korea	73	5.38%
5	Russia	54	3.98%

but also the type locality of *A. japonicus* (Liao, 1997). Graphs indicating international comparisons of *A. japonicus* literature numbers and cooperative relationships were plotted (Figure 2). A total of 58 countries worldwide have been involved in *A. japonicus* research. However, only 115 international collaborations in the form of literature have been recorded, which is only 8.47% of the total literature. These data indicate that there is a huge scope for international collaboration in *A. japonicus* research.

Analysis of participating journals

The Journal Citation Reports (JCR) Quartile and Impact Factor (IF) of journals often represent the quality of the research output (Law and Leung, 2020). The top 10 journals published in the field of *A. japonicus* are listed in Table 3 based on the database and comparison with the JCR 2020. More than 297 academic journals have published articles on *A. japonicus* research. *Fish and Shellfish Immunology* (Q1; IF2020, 4.581) published the most articles on the study of *A. japonicus* (119 articles, 8.76%), followed by *Aquaculture* (Q1; IF2020, 4.242; 113

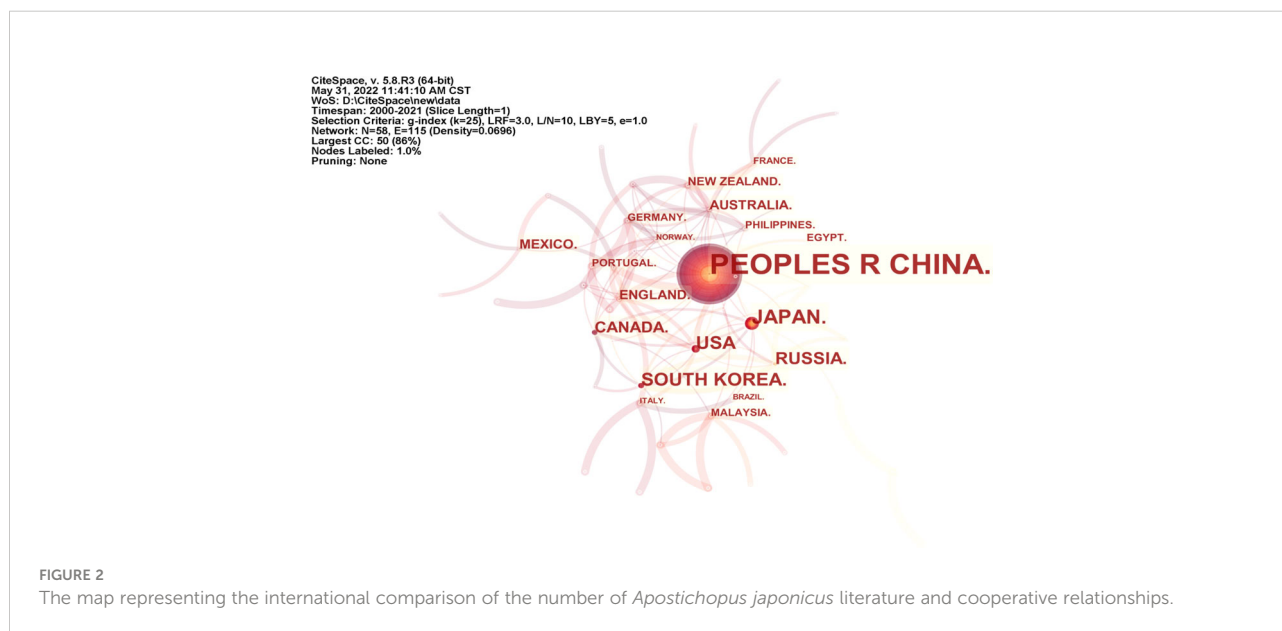


FIGURE 2 The map representing the international comparison of the number of *Apostichopus japonicus* literature and cooperative relationships.

TABLE 3 The most active journals with publication volume on *Apostichopus japonicus* search from 2000 to 2021.

Ranking	Journal abbreviation	Country	Count	JIF quartile	IF2020
1	<i>Fish Shellfish Immunol.</i>	England	119	Q1	4.581
2	<i>Aquaculture</i>	Netherlands	113	Q1	4.242
3	<i>Aquac. Res.</i>	England	98	Q2	2.082
4	<i>J. Oceanol. Limnol.</i>	China	40	Q4	1.265
5	<i>J. Ocean Univ. China</i>	China	31	Q4	0.913
6	<i>Dev. Comp. Immunol.</i>	England	30	Q1	3.636
7	<i>Fish. Sci.</i>	Japan	29	Q3	1.617
8	<i>Comp. Biochem. Physiol., Part D: Genomics Proteomics</i>	USA	28	Q3	2.674
9	<i>Food Chem.</i>	England	28	Q1	7.514
10	<i>Aquac. Int.</i>	Netherlands	27	Q2	2.235

articles, 8.32%) and *Aquaculture Research* (Q2; IF2020, 2.082; 98 articles, 7.22%). Notably, in 2019, JCR imposed a short penalty on the Q1 regional journal *Fish and Shellfish Immunology* for self-citing rate issues. As a result, the level of publications and research in the area of *A. japonicus* has declined in the short term. In comparison with other journals, articles on *A. japonicus* were more likely to be accepted by these active journals.

Analysis of the influence of the literature

Highly cited articles in the field represent the existence of more interest and affirmation by practitioners in the current state of research in a particular direction. We counted the papers published in the field of *A. japonicus* in the past 21 years. The 10 most influential academic papers were selected based on the

number of citations as of 1 April 2022 (Table 4). The research directions of these 10 papers were briefly classified, and the general research directions were sea cucumber bioactive, fucosylated chondroitin sulfates (FCSs), diseases, growth performance, probiotics, aestivation, body wall collagen, and transcriptome sequencing.

Analysis of research directions

In the analysis of research directions, *A. japonicus* research is more focused on biology, marine science, and aquaculture. Based on the Web of Science subject classification method, the related literature of *A. japonicus* was classified (Table 5). Nearly 97% of these studies involved life sciences and biomedical research, with almost no research related to industry or

TABLE 4 The 10 most influential papers in the field of *Apostichopus japonicus* from 2000 to 2021.

Author	Title	Frequency	Year
Bordbar, Sara; Anwar, Farooq; Saari, Nazamid	High-value components and bioactives from sea cucumbers for functional foods-a review	404	2011
Duarte, MER; Cardoso, MA; Noseda, MD; Cerezo, AS	Structural studies on fucoidans from the brown seaweed <i>Sargassum stenophyllum</i>	234	2001
Chen, Shiguo; Xue, Changhu; Yin, Li'ang; et al.	Comparison of structures and anticoagulant activities of fucosylated chondroitin sulfates from different sea cucumbers	213	2011
Deng, Huan; He, Chongbo; Zhou, Zunchun; et al.	Isolation and pathogenicity of pathogens from skin ulceration disease and viscera ejection syndrome of the sea cucumber <i>Apostichopus japonicus</i>	195	2009
Dong, YW; Dong, SL; Tian, XL; Wang, F; Zhang, MZ	Effects of diel temperature fluctuations on growth, oxygen consumption and proximate body composition in the sea cucumber <i>Apostichopus japonicus</i> Selenka	165	2006
Zhang, Qin; Ma, Hongming; Mai, Kangsen; et al.	Interaction of dietary <i>Bacillus subtilis</i> and fructooligosaccharide on the growth performance, non-specific immunity of sea cucumber, <i>Apostichopus japonicus</i>	161	2010
Yang, HS; Yuan, XT; Zhou, Y; Mao, YZ; Zhang, T; Liu, Y	Effects of body size and water temperature on food consumption and growth in the sea cucumber <i>Apostichopus japonicus</i> (Selenka) with special reference to aestivation	178	2005
Zhao, Yancui; Zhang, Wenbing; Xu, Wei; et al.	Effects of potential probiotic <i>Bacillus subtilis</i> T13 on growth, immunity and disease resistance against <i>Vibrio splendidus</i> infection in juvenile sea cucumber <i>Apostichopus japonicus</i>	151	2012
Saito, M; Kunisaki, N; Urano, N; Kimura, S	Collagen as the major edible component of sea cucumber (<i>Stichopus japonicus</i>)	153	2002
Du, Huixia; Bao, Zhenmin; Hou, Rui; Wang, Shan; et al.	Transcriptome sequencing and characterization for the sea cucumber <i>Apostichopus japonicus</i> (Selenka, 1867)	132	2012

TABLE 5 Classification of the main research areas of *Apostichopus japonicus* based on the subject classification method of Web of Science (WoS) from 2000 to 2021.

Ranking	Research areas	Count	Proportion
1	Fisheries	512	37.70%
2	Marine Freshwater Biology	339	24.96%
3	Immunology	179	13.18%
4	Food Science Technology	175	12.89%
5	Biochemistry Molecular Biology	166	12.22%

economy. It will be helpful for us to follow up on the subdivision of the research direction of *A. japonicus* and no longer consider the research on industrial economy, history and culture, and diet.

Analysis of main keywords

In the keyword set of a large number of professional papers in the same discipline, hidden clues can be found about the current status of research, research hot spots, and development trends (Yin et al., 2009). Therefore, quantitative and visual analysis of keywords in *A. japonicus* research literature is helpful in mining knowledge in this field.

The term frequency-inverse document frequency weighted algorithm was used to calculate the importance of a keyword in a set of all keywords, highlighting key nodes and important connections, and form keyword clusters (Chen et al., 2015). The bibliography was imported into CiteSpace software, and synonym merging and keyword nonsense deletion were performed to achieve a symbiotic map of 682 keywords consisting of nodes and 1,393 links (Figure 3). One of the nodes represents a keyword. The larger the circle of nodes, the

more frequently the keyword is cited, and the more frequently it can be considered a research hot spot in the *A. japonicus* field. As shown in Figure 3, the largest keyword node is *A. japonicus*, while the other nodes are more widely distributed mainly along the three branches of the distribution. In combination with the keyword frequency ranking data (Table 6), *A. japonicus* hot spots can be identified. The main keywords that appear in three directions are growth, protein, body wall, immune response, temperature, gene expression, and purification.

Clustering graphs can accurately reflect the knowledge structure of different research directions (Rodriguez and Laio, 2014). We used the logarithmic likelihood ratio algorithm for keyword clustering. This algorithm can accurately reflect the contribution of low-frequency keywords to clustering and overcome the inaccuracy of the classical feature vector selection algorithm in low-frequency word estimation (Lin and Tang, 2009). By adjusting the contrast of the color blocks, a keyword network clustering map was formed (Figure 4). The hot spots in *A. japonicus* research over the past two decades can be briefly classified into the following categories: 1) growth, including keywords such as temperature, energy budget, and organic matter; 2) FCS, including body wall, *in vitro*, and glycosaminoglycan; 3) *Apostichopus japonicus*, including

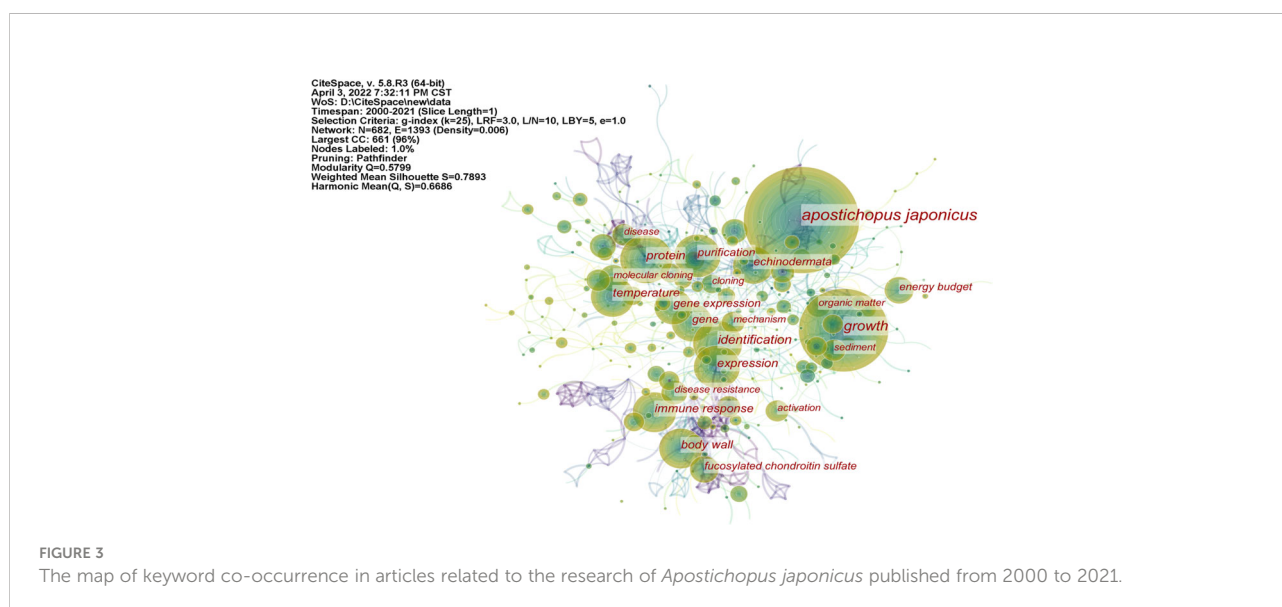


TABLE 6 The 20 most frequently used keywords in articles related to *Apostichopus japonicus* research published from 2000 to 2021.

Ranking	Keyword	Frequency	Centrality	Ranking	Keyword	Frequency	Centrality
1	<i>Apostichopus japonicus</i>	502	0.08	11	purification	74	0.11
2	growth	224	0.03	12	gene	72	0.04
3	identification	124	0.05	13	energy budget	53	0.04
4	protein	104	0.07	14	fucosylated chondroitin sulfate	53	0.05
5	expression	93	0.09	15	mechanism	44	0.05
6	body wall	89	0.1	16	cloning	43	0.07
7	immune response	88	0.01	17	activation	41	0.05
8	temperature	79	0.06	18	disease	41	0.02
9	gene expression	75	0.02	19	disease resistance	40	0.01
10	Echinodermata	74	0.13	20	sediment	40	0.03

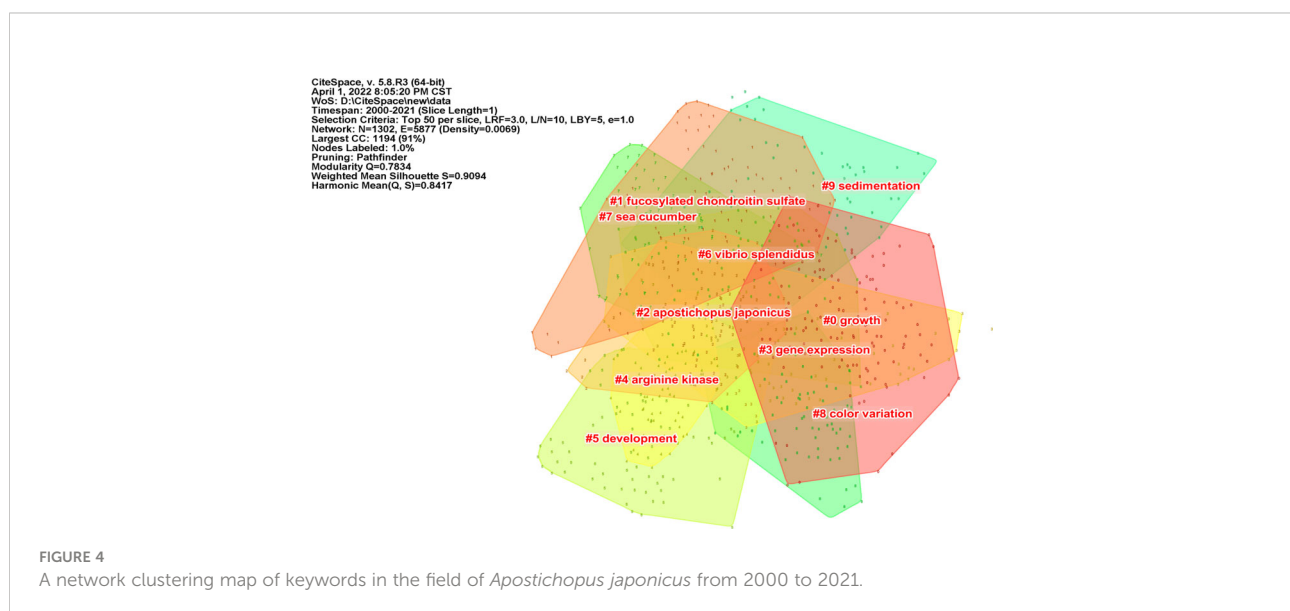
identification, protein, expression, and gene; 4) arginine kinase, including purification, mechanism, binding, phosphagen kinase, and inactivation; 5) *Vibrio splendidus*, including collagen, bacteria, triterpene glycoside, and resistance; 6) sea cucumber, including anticoagulant activity, NF-kappa B (NF- κ B), peptide, and fucoidan. Some clusters generated by software analysis do not cover the entire content of the knowledge structure, and these clusters need to be properly integrated or renamed.

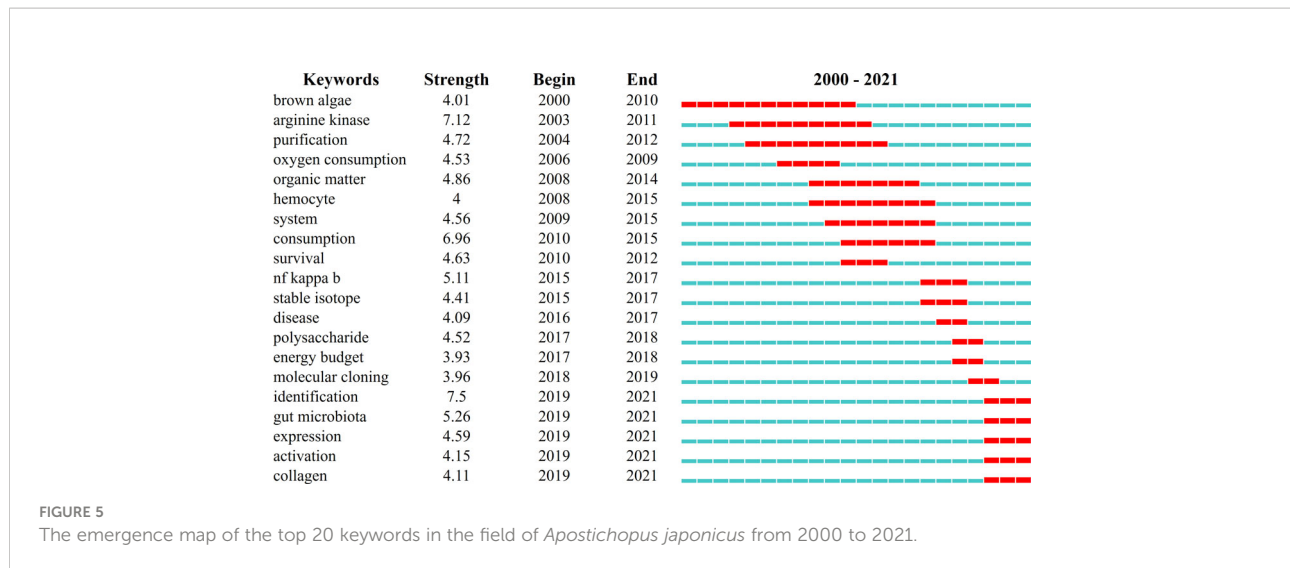
In terms of keyword emergence time, CiteSpace uses Kleinberg's burst word monitoring algorithm, which is based on the vending machine model, to model keyword frequency over different periods (Kleinberg, 2003). The duration of the main keyword emergence varies, as shown in Figure 5. The emergence lasted from 2000 to 2010 for brown algae, 2003 to 2011 for arginine kinase, 2010 to 2015 for consumption, 2015 to 2017 for NF- κ B, and 2018 to the present for identification. These keywords have strong intensity and long duration and are all important in any research period. Recently emerging

keywords included gut microbiota, activation, and collagen, which may be the main direction and technical methods of current or future research.

Conclusion

As a condensation of literature knowledge, keywords deserve to be further classified and studied. The results of the software analysis can provide us with some assistance and evidence, but they do not fully represent the actual research status. Therefore, it is necessary to integrate all of the analyses and own experience to reach a final conclusion. Based on the network clustering map of keywords in Figure 4, the research direction in the *A. japonicus* domain was gradually clarified after integrating the citation frequency (Figure 3 and Table 6), occurrence time, and intensity (Figure 5) of keywords and the progress of large research teams. It was divided into six departments: genetics and breeding, growth





and development, immunology and disease, aestivation, regeneration, and food processing.

Research on the genetics and breeding of *Apostichopus japonicus*

High-quality seedlings are important for the survival and development of the aquaculture industry. Research into the genetics and breeding of *A. japonicus* should also be the most concerning work in the *A. japonicus* industry. Genetics and breeding include but are not limited to genetic marker development, genetic linkage map construction, and genetic mechanism analysis of economic traits. 1) Studies on the genetic marker development of *A. japonicus*. The molecular genetics of *A. japonicus* concentrates on the development of microsatellite markers and single-nucleotide polymorphisms (SNPs). Microsatellite labeling technology is used for sifting through microsatellite locations and detecting them after PCR amplification. Kanno et al. (2005) have used magnetic bead enrichment methods by hybridization to develop 20 polymorphic microsatellite markers for sea cucumbers, which will be helpful for further research on the genetic structure and reproductive isolation of sea cucumbers. SNPs are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide (National Library of Medicine, 2022). Based on the assembly transcriptome, Zhou et al. (2014) identified 142,511 high-quality SNPs. Attempts were made by Kang et al. (2011) to identify SNPs and to analyze differences associated with SNP genotypes between green and red color variants using heat shock protein (HSP)70 as the target gene. 2) Studies on the genetic linkage map construction of *A. japonicus*. Most of our earlier knowledge on echinoderm genomics came from the sea urchin

Strongylocentrotus purpuratus and sea star *Acanthaster planci*; the need for the complete genome of *A. japonicus* is becoming increasingly urgent. The whole genome of *A. japonicus* released by team Hongsheng Yang in 2017 is a more complete one in recent years (Zhang X. J. et al., 2017). Li et al. (2018b) then updated the whole-genome landscape, perfecting the development of the whole genome of *A. japonicus*. 3) Studies on the genetic mechanism analysis of economic traits of *A. japonicus*. Growth rate, body wall thickness and flesh yield, and stress resistance are the most important economic traits of *A. japonicus*. Chen et al. (2020) tried to identify and screen potential molecular markers associated with the quantitative traits of “Anyuan No. 1” by miRNA-mRNA integrated analysis for future selective breeding and new seed creation in sea cucumbers. “Anyuan No. 1” is exactly the new generation breed of the Chinese, with weight, number of parapodium, and dressing-out percentage as the main target traits. The stress resistance includes indicators of a low-salt tolerance, high-temperature tolerance, and antibacterial infection. Song et al. (2012) compared the growth traits of different pedigrees under low-salt environment by means of line selection, and finally, nine low salt-tolerant pedigrees were obtained. Zhao H. et al. (2014) analyzed the survival rate and HSP gene expression characteristics under high-temperature stress in the offspring of a high temperature-oriented selection population of *Sargassum* and preliminarily validated the heritability of heat tolerance traits in the selection population.

Research on the growth and development of *Apostichopus japonicus*

Researchers have focused on the growth performance of *A. japonicus*. The research direction of growth performance mainly includes feed formulation, temperature, salinity, and

cocultivation environment. 1) Studies on the effect of feed formulation on the growth and development of *A. japonicus*. Qin Zhang and Yancui Zhao provided evidence that the addition of probiotic *Bacillus subtilis* T13 and prebiotic fructooligosaccharides to the feed has a synergistic effect on improving immunity and disease resistance of *A. japonicus* (Zhang et al., 2010; Zhao et al., 2012). According to the specific growth rate of sea cucumber, the formula of 75% bivalve feces and 25% powdered algae was the best diet for sea cucumber culture (Yuan et al., 2006). 2) Studies on the effect of temperature and salinity on the growth performance of *A. japonicus*. Dong et al. (2006) studied the effects of constant or variable temperature on the growth, proximate body composition, and oxygen consumption of juvenile sea cucumbers. Moreover, the appropriate temperature for *A. japonicus* growth is between 12°C and 21°C, the optimum temperature is 16°C–18°C, and the diel fluctuating temperature model promotes the growth of juvenile sea cucumbers and can be applied to the large-scale culture of *A. japonicus*. A temperature range of 21°C–24°C and a salinity of 30 are considered optimal for the early development of the red *A. japonicus* (Li and Li, 2010). 3) Studies on the effect of coculture environment on the growth performance of *A. japonicus*. The coculture of juvenile charm abalone *Haliotis discus hannai* and sea cucumber can reduce the content of inorganic nitrogen in water and promote synergistic growth (Kang et al., 2003). It can be used as an alternative culture method during the overwintering period of abalone farms.

Research on the immunology and disease of *Apostichopus japonicus*

The immunological research of *A. japonicus* mainly covers the epidemiology of pathogenic microorganisms, immunology and pathology of aquatic organisms, aquatic disease prevention, and control technology. 1) Pathogenic microorganism epidemiology mainly studies the epidemiological characteristics of diseases of farmed species, clarifies the regulatory effect of key environmental factors on pathogenic infection, reveals the molecular mechanism of epidemic outbreak and epidemic, and provides an analysis of the pathogenic principle of the main pathogens and the immune escape mechanism of the pathogens in the host. *V. splendidus* is the main causative agent of skin ulceration syndrome (SUS), which is the most common and serious disease in sea cucumber culture (Zhang et al., 2014). In the early stage of SUS, *A. japonicus* has the phenomenon of shaking its head, slow response, swelling of the mouth cannot be contracted; in the middle stage, the body of *A. japonicus* shrinks, the flesh spines turn white, small ulcers appear on the epidermis, and drainage of dirt; in the end stage, the epidermis ulcerates widely until death and autolysis (Li et al., 2013; Yang et al., 2016). The main

causative factors identified at present of *V. splendidus* include adhesion molecules, iron absorption systems, and some extracellular products with toxicity (Zhang et al., 2016). Adhesion molecules in charge of contacting and binding to receptors include flagella, lipopolysaccharide, and outer membrane proteins (Dai et al., 2022). To cover the iron requirements for growth and reproduction, iron absorption systems have developed, including iron carriers and ferritin (Huang B. W. et al., 2021). Extracellular products can help defend the host immune killings, such as extracellular proteases and hemolysins (Binesse et al., 2008). 2) Immunology and pathology of aquatic organisms provide information about the changes in morphological structure, function, and metabolism of immune organs and immune cells in response to pathogenic microbial infection, revealing the occurrence and development of diseases. The immune system of *A. japonicus* in response to *V. splendidus* infection mainly consists of coelomocytes, immune factors, and gut microbiota. The defense means adopted by the coelomocytes when facing the invasion of pathogenic microorganisms are abundant, including chemotaxis (damaged cells release information to attract a large number of inflammatory cells, triggering inflammation) (Lv et al., 2022) and programmed cell death (apoptosis, autophagy, and pyroptosis may exist in *A. japonicus*) (Shao et al., 2016; Shao et al., 2019; Shao et al., 2020). The immune factors in *A. japonicus* mainly include Toll-like receptor (Sun H. J. et al., 2013), myeloid differentiation factor (Lv et al., 2019), interleukin-1 receptor-associated kinase (IRAK)-1 and IRAK-4 (Lu et al., 2015; Cui et al., 2018), NF-κB subunit (Wang et al., 2013), and signal transduction and activator of transcription-5 (Shao et al., 2015). Research on gut microbiota has been a hot topic in recent years, and we have mentioned above that the timing of their heat emergence may continue. Gut microbiota forms a biological barrier that restricts pathogen colonization in the intestine and enhances the original nonspecific immune function of *A. japonicus* (Li et al., 2012; Chi et al., 2014). *A. japonicus* gut microbiota provides a timely and accurate response to the occurrence of disease, which is directly reflected in the change of flora structure after the disease (Zhang Z. et al., 2018; Zhang et al., 2019). 3) Aquatic disease prevention and control technology aim to solve the root cause of disease problems in aquaculture, which requires the full management of all aspects such as disease-resistant seedlings, immune enhancers, symptomatic medication, and daily monitoring of the water environment (Li, 2021). “Anyuan No. 1” and “Shenyou No. 1” are new *A. japonicus* breeds with better economic performance and disease resistance that have been cultivated in China in recent years, and the development of new breeds can effectively improve breeding efficiency (Chen et al., 2020; Wang Z. P. et al., 2021). Immune enhancers improve nonspecific immunity and suppress invading pathogens in cultured animals to improve survival and growth rates. Numerous known substances can be used as immune

enhancers for *A. japonicus*, mainly classified as Chinese herbal preparations (Sun et al., 2015), polysaccharides (Gu et al., 2011), and probiotics (Zhao et al., 2012). The overuse of antibiotics in animal farming is costly and undesirable and has threatened the human living environment (Harikrishnan et al., 2011). The use of antibiotic alternatives for pathogen suppression is imperative, such as the use of antivirulence biologics (Zhang S. S. et al., 2017), phages (Katharios et al., 2017), and probiotics.

Research on the aestivation of *Apostichopus japonicus*

Aestivation of *A. japonicus* has also been widely studied. Metabolic rate depression is a very common mechanism for animals to escape from environmental stress (Brooks and Storey, 1997). For *A. japonicus*, the temperature is the principal environmental factor that determines its growth rate (Yang et al., 2005). Moreover, aestivation is the main strategy for *A. japonicus* to reduce its metabolic rate to resist high temperatures (Du et al., 2013). Studies on aestivation in *A. japonicus* have focused on histomorphology, physiobiology, and molecular biology (Yuan et al., 2007). 1) Studies on the histomorphology of *A. japonicus* during aestivation. According to the changes in the gut and respiratory trees of *A. japonicus*, the aestivation process can be roughly divided into four stages: active period, aestivation period, deep aestivation period, and recovery period (Cheo, 1963). The most obvious physiological manifestation of *A. japonicus* during aestivation is the cessation of feeding and activity (Chen et al., 2016), which causes degradation of the digestive system (Gao et al., 2009) and negative body mass growth to maintain minimum metabolic requirements (Zhao Y. et al., 2014). Wang et al. (2007) showed that the ratio of the digestive tract length to body length was only 0.8–1.1 during the aestivation from August to October, while the ratio was 2.7–5.9 for the normal growth period from January to May. Gao (2008) reported that the relative digestive mass of the intestine during aestivation was only 8.2%–35.8% of the annual maximum. Therefore, shortening the aestivation period can effectively improve the benefits of the cultivation process. 2) Studies on the physiobiology of *A. japonicus* during aestivation. Depending on the daily food intake of individuals, Yang et al. (2005) reported that the starting temperature at which medium and large *A. japonicus* (72.3–139.3 g) entered aestivation was 24.5°C–25.5°C and that of the small individual (28.9–40.7 g) was 25.5°C–30.5°C. They continued to determine the effect of water temperature on oxygen consumption rate (OCR) and ammonia-N excretion rate (AER) of aestivated *A. japonicus* using the Winkler and Hypobromite methods. Both OCR and AER of mature (large, 148.5 ± 15.4 g; medium, 69.3 ± 6.9 g) individuals peaked at 20.8°C, while the OCR of immature (small, 21.2 ± 4.7 g) individuals continued to increase with temperature and even beyond the aestivation temperature, while their AER peaked at 25.8°C (Yang

et al., 2006). The results of previous studies have shown that both coelomocytes and immune enzymes of *A. japonicus* underwent significant changes during aestivation (Wang et al., 2008). Liu et al. (2016a) reported a significant effect of temperature on both immuno-enzyme activities [Superoxide dismutase, catalase, total antioxidant capacity (T-AOC)] and metabolic enzyme activities (pyruvate kinase (PK), hexokinase, malate dehydrogenase, lactate dehydrogenase (LDH)) in the non-aestivating group of *A. japonicus*, while the effects on T-AOC, PK, and LDH activities in the aestivating group were not significant. 3) Studies on the molecular biology of *A. japonicus* aestivation. At present, the molecular biology research on aestivation is still in its infancy, and the research content is mostly distributed in a dot-like distribution without systematization. Li et al. (2018b) reported that transcriptional factors Klf2 and Egr1 were identified as key regulators of aestivation, probably exerting their effects through a clock gene-controlled process. Yang (2017) investigated the changing pattern of *A. japonicus* 5-hydroxytryptamine (5-HT) receptor (Aj5-HTR) in the aestivation cycle and its function in metabolic regulation and, based on the results, elucidated the relationship between 5-HT and its receptor 5-HTR and the existence of metabolic regulation of aestivation in *A. japonicus*. Chen and Storey (2014) used high-throughput sequencing technology to detect and analyze the miRNA expression patterns in the intestine and respiratory tree before and after aestivation and screened out the differentially expressed miRNAs. They found that miR-124, miR-124-3p, miR-79, miR-9, and miR-2010 were significantly overexpressed during deep aestivation, and these miRNAs may play an important role in inhibiting the metabolic rate of *A. japonicus* during aestivation (Chen et al., 2013). In the follow-up study, they used tandem mass tag labeling followed by an immobilized metal-chelate affinity chromatography enrichment method to map aestivation sensitive changes in the *A. japonicus* intestinal phosphoproteome (Chen et al., 2016). The current research, including the above parts, has not clarified the molecular regulation mechanism of *A. japonicus* aestivation, which needs to be further broadened and deepened.

Research on the regeneration of *Apostichopus japonicus*

A growing number of scientists are attempting to demystify the organ regeneration process in invertebrates and lower vertebrates and determine whether the methods that trigger such regeneration can be applied to vertebrates (Tanaka and Reddien, 2011; Marques et al., 2019). The echinoderms to which sea cucumbers belong are grouped in the Duteromata evolutionary branch of animals and are therefore closely related to vertebrates in terms of phylogeny. Adult sea cucumbers are a useful model for organ regeneration (Garcia-Ararras et al., 2019). Current research on the regeneration of *A.*

japonicus is mainly focused on digestive tract regeneration (Garcia-Arraras and Greenberg, 2001), and a few of them involve coelomocyte and longitudinal muscle band (LMB) regeneration. 1) Studies on digestive tract regeneration in *A. japonicus*. The regeneration process of the digestive tract can be divided into the rudiment formation stage, intestinal lumen formation stage, differentiation stage, and growth stage (Nie and Li, 2006). Only the calcareous ring and the stump of the pharynx-esophagus and cloaca remained in the body cavity after gutting, and two rudiments are formed by the stump of the pharynx-esophagus and cloaca in the anterior and posterior parts of the body, respectively. They grow along the free edge of the thickened mesentery toward the middle of the body, penetrate the mesenchyme, and form a fine digestive tract (Leibson, 1992). The thickened mesentery allows *A. japonicus* to regenerate the missing part of the intestine between the two ends much faster in order to feed earlier (Mashanov and Garcia-Arraras, 2011). Garcia-Arraras et al. (1998) described the spatial and temporal patterns of cellular events that occur during intestinal regeneration after chemically induced evisceration. It is also essential to investigate the molecular mechanism of the digestive tract regeneration in *A. japonicus*. The first signs of somatic epithelial cell activation on the molecular level were detected as early as 24 h after organ culling, with increased the transcription of genes involved in transcription, translation, and protein transport (Quispe-Parra et al., 2021). Data obtained by metabolomic analysis showed that the accumulation of nutrients in the residual esophageal tissue occurred after 3 days post-evisceration (dpe) (Sun et al., 2017a). The accumulation of energy reserves and their further utilization during regeneration are regulated by deacetylation (Sun et al., 2018). The expression of Hox1 and Hox3 was recorded as increased during this period, which proves that the formation site of the anterior part of the intestine is determined (Sun et al., 2017b). While Hox9/10 started to be expressed after 7 dpe, the site of formation of the posterior part of the intestine was marked (Sun et al., 2013b). Yuan et al. (2019) reported that the Wnt signaling pathway is the only pathway under positive selection in regenerating echinoderms and the only pathway enriched by differentially expressed genes during intestinal regenerating. An increase in the number of Wnt4 and Wnt6 transcripts was recorded after 7 dpe (Sun et al., 2013a). At 14–21 dpe, the main feature of this phase is the redifferentiation of enterocytes. Expression of Hox9/10 and Hox11/13 continued to increase, and marking of the anterior–posterior axis continues. The main processes occurring in *A. japonicus* during intestinal tube formation are extracellular matrix (ECM) remodeling, cell dedifferentiation, cell migration, cell proliferation, and apoptosis (Dolmatov, 2021). Two matrix metalloproteinase (MMP) genes, *MMP-2* and *MMP-16*, may regulate the interaction between ECM components and growth factors by performing targeted proteolysis of ECM proteins and other biomolecules (Miao et al., 2017). The regeneration process

requires a regulation between cell proliferation and cell death. Apoptotic cells greatly influence the behavior of the surrounding cells through phagocytosis and proliferation, as well as by activating the Wnt signaling (Kawamoto et al., 2016). The Wnt signaling pathway was activated during intestinal regeneration in sea cucumbers. The expression of Wnt7 and Wnt8 peaked after 1–3 dpe, while the number of Wnt6 transcripts was highest at 7 dpe and was maintained for a long time (Sun et al., 2013). 2) Studies on coelomocyte and LMB regeneration in *A. japonicus*. *A. japonicus* required depletion and regeneration of coelomocytes for effective innate immune mechanisms (Smith et al., 2010; Li et al., 2019). Available studies have shown that coelomic fluid and coelomocyte regenerate rapidly after the removal of viscera from sea cucumbers, returning to normal levels after 2 and 6 h, respectively (Li et al., 2018; Shi et al., 2020). Dolmatov et al. (1996) demonstrated that new muscle bundles were derived from coelomic epithelial cells covering LMBs. The migration of coelomic epithelial cells to damaged LMBs and their myogenic transformation are the basic mechanisms of muscle regeneration. Ginanova (2007) reported that the coelomic epithelium of the body wall and the coelomic epithelium of the muscle of *A. japonicus* are involved in the regeneration of muscle tissue at the same time and have an important role in the recruitment of myogenic cell pools. The work by Qin et al. (2015) illustrates that the S7 subunit of the 19S gene or the S7-based assembled 26S proteasome may be involved in the regulation of cell migration and cell cycle during the regeneration of the *A. japonicus* body wall.

Research on the food processing of *Apostichopus japonicus*

Sea cucumber is delicious and nutritious. They are highly edible and have medicinal value. The medical value of sea cucumbers still has enormous scope for development and is not yet widespread. As an important part of the entire industrial chain of sea cucumbers, food engineering is also a hot spot in the field of *A. japonicus* research. Sea cucumber derivatives have many types, including polysaccharides, saponins, sea cucumber bioactive peptides, and many other biologically active compounds. At first, sea cucumber polysaccharides extracted from the body wall of sea cucumbers are unique to sea cucumber species, which are composed mainly of holothurian glycosaminoglycan and holothurian fucan (Jin et al., 2019). Current research is mainly focused on anticoagulation, antitumor, antiviral, and other directions (Pomin, 2014). 1) Study on the anticoagulation mechanism of sea cucumber polysaccharides. FCSs have stronger anticoagulant activity than sulfated fucan (Chen et al., 2011; Luo et al., 2013). The difference in the anticoagulant properties of FCSs is mainly attributed to their different sulfation patterns. 2) Study on the antitumor effect of sea

cucumber polysaccharides. Low-molecular-weight FCSs could significantly inhibit the growth and metastasis of Lewis lung carcinoma in mice in a dose-dependent manner (Liu X. X. et al., 2016). *A. japonicus* acid mucopolysaccharide (AJAMP) has an effective inhibitory effect on experimental hepatocellular carcinoma in rats, and the antitumor mechanism of AJAMP can protect immune organs, promote the proliferation of immune organs and tissues, and enhance cellular immunity (Song et al., 2013). 3) Study on the antiviral activity of sea cucumber polysaccharides. Through screening, the Academician of the Chinese Academy of Engineering Zhu Beiwei obtained three polysaccharides, namely, sea cucumber sulfated polysaccharide, fucoidan from brown algae, and iota-carrageenan from red algae, which have significant antiviral activities. The three antiviral polysaccharides could be employed for the treatment and prevention of coronavirus disease 2019 (COVID-19) (Song et al., 2020). Secondly, as the most important and abundant secondary metabolites in sea cucumbers, the research on saponins is also one of the hot topics (Bahrami and Franco, 2015; Bahrami and Franco, 2016). Due to their numerous and positive bioactivities, sea cucumber saponins are now high-economic value natural compounds with great market potential in the fields of medicine (Aminin et al., 2015; Dai et al., 2020), healthcare (Li et al., 2020), and cosmetics (Osborn et al., 2011). In addition, studies on bioactive peptides and other biologically active compounds of sea cucumber have shown that they have lots of functions beneficial to the human body (Zhu et al., 2012; Pangestuti and Arifin, 2018; Zhang L. Y. et al., 2018).

Discussion

This report reviews the history of *A. japonicus* research and the available scientific data from 2000 to 2021. Clearly, sea cucumbers should be considered a key component of aquaculture in terms of either economic or scientific value. We have divided the direction of *A. japonicus* research into six departments, namely, genetics and breeding, growth and development, immunology and disease, aestivation, regeneration, and food processing, which have independent and interlinked characteristics. These six research departments cover most of the problems that occurred during the production and processing of *A. japonicus*.

The five other research departments all serve the sea cucumber industry, and only the research on regeneration serves humans directly. Many tools and references can help improve the knowledge of regeneration phenomena in sea cucumbers and contribute to knowledge sharing. Biologically, regeneration is the process of displacing or restoring damaged or lost cells, tissues, organs, or even entire parts to respond resiliently to environmental fluctuations (Birbrair et al., 2013; National Institute of General Medical Sciences, 2021). Regeneration of tissues and organs depends on obtaining the cells required to form the new structure. These cells usually originate from two origins: 1)

resident stem cells or 2) mature cells close to the injury site that lose their phenotype and dedifferentiate (Garcia-Ararras, 2017). Each metazoan species has the ability to regenerate and differs greatly (Carlson, 2007; Lindsay, 2010). In Echinodermata, tissue regeneration is well represented in Asterozoa, Holothurozoa, and Echinozoa to a higher degree (Carnevali et al., 1998). Among them, sea cucumbers show superb regenerative ability and can quickly regenerate various new functional internal organs when the environmental conditions are suitable, which is much greater than the ability of sea stars and sea urchins (Zhang et al., 2017). Therefore, they believe that studying the regeneration of sea cucumbers could inspire humans to find the key to initiating tissue regeneration *in vivo*. In contrast to other species, such as zebrafish (Yan and Gu, 2013; Marques et al., 2019), where various models of damage have been developed for the study, *Schmidtea mediterranea* (Lewallen and Burggren, 2022), where the metabolic cost of regeneration has been further investigated, and *Eublepharis macularius* (Austin et al., 2021), which has been found to regenerate spontaneous neurons in damaged brains, the road to regeneration research of sea cucumbers is long and difficult.

In summary, differences were observed based on the comparison of research power between regions and teams, and more extensive support is needed in regions with more developed industries or greater resource abundance. Governments or organizations are encouraged to 1) promote the development of the *A. japonicus* industry through the development or implementation of policies; 2) further participate in the whole process of research, production, and processing of *A. japonicus*; and 3) strengthen international exchange and cooperation to bring economic benefits to farmers in suitable breeding areas through technology sharing.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JC, MG, ZL. The first draft of the manuscript was written by JC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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