An Evaluation of the Coupling Coordination of Technological Innovation System in China’s Marine Biopharmaceutical Industry

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Abstract The marine biopharmaceutical industry (MBI) has been considered as an important part of the blue economy. The high-quality development of this industry depends on the high-level coordinated development of technological innovation system (TIS). In the present study, the coupling mechanism of industrial innovation input subsystem and innovation output subsystem was analyzed for the first time. On this basis, the development level and coupling coordination level of TIS in China’s MBI during 2008-2018 were empirically evaluated with the capacity coupling coordination model. Then, the obstacle factors were diagnosed and recognized with the obstacle model. The results showed that the innovation input index fluctuated at a low level in China’s MBI. The innovation output index has basically maintained a growth trend, whereas the quality of development was not high. Although the coupling coordination level of TIS showed a positive change as mild disordered → primary coordinated → well-coordinated, the development type of innovation system has changed from the lagging output of innovation into the lagging input of innovation. Insufficient input of innovation factors remained the main obstacle to the improvement of coordination level. Based on the above analysis, suggestions were put forward from the perspectives of policy and fund guarantees to improve the coupling coordination level in China’s MBI.

Key words marine biopharmaceutical industry; technological innovation system; subsystem coupling; coordinated development; obstacle factor

1 Introduction

The special aquatic environment of the ocean breeds unique marine biological resources, which bring new hope for solving the major and difficult diseases that seriously threaten human health (Wang et al., 2009; Hassan et al., 2017). The interest in the discovery of health-promoting substances from marine organisms has been rising for decades (Rengasamy et al., 2020). Since 2008, the rate of separation of natural products from the ocean has exceeded 1000 per year, with 1407 new marine natural products discovered in 2020 (Carroll et al., 2022). The global pandemic of COVID-19 has made people more aware of the importance of health. Drugs from the sea are expected to provide a ‘blue drug’ solution plan for epidemic prevention and control. The marine biopharmaceutical industry (MBI) has become a strategic highland for international competition in the pharmaceutical industry. In recent years, China put forward its national strategy of the ‘Blue Drugs Bank’ in a timely manner to aid the rise of the MBI in China. At present, China has become the main discoverer of marine natural products. And the number of newly discovered marine natural products is about 6700, accounting for 20% of the world (Zhu et al., 2019) from which 10 marine drugs have been independently developed and approved for marketing by China (Zhang et al., 2018; Wang et al., 2019). In addition, some potential marine drugs, such as Chitosan Ester (phase III), Polymannuroguluronate Sulfate (phase II), D-Polymannuronate Sulfate (phase II) and FPS (phase II), have entered the clinical trial. At present, a number of the key screening technologies for basic research on marine drugs in China have reached an advanced international level. The industry is undergoing a ‘leapfrog development’ stage, from basic research to industrialization. However, at present, there are still many prominent problems in MBI...
development, such as insufficient funding in research and development (R&D), lack of high-level technical talents, and an imperfect innovation policy system (Fu et al., 2018; Huang and Zhou, 2015). The industry has not formed a systematic and stable innovation factor input system yet. Natural products have the characteristics of strong leading and weak druggability. From 1981 to 2019, 1881 new drugs were approved for marketing worldwide, but only 71 were directly produced from natural products, accounting for 3.8% (Newman and Cragg, 2020). As for marine natural products, the rate is even lower. Limited by the insufficient innovation input and the weak links between innovation subjects, the R&D of marine drugs in China is mostly in the stage of marine natural product discovery. And the industry confronts the development dilemmas of a low industrialization level, lack of competitiveness of marketed marine drugs compared with existing indication drugs, and a low market share of new products. Finally, the economic benefits of innovation achievements are poor, which is difficult to support industrial innovation input (Fu et al., 2015).

The key to enhancing industrial competitiveness lies in technological innovation. Industrial technological innovation is the transformation process of innovation resources from innovation input to intermediate innovation output and final innovation output (Acs et al., 2002). The coordination relationship between industrial innovation input and output is destined of great importance due to the technology-intensive characteristics of the MBI. At present, the innovation input and output subsystems of China’s MBI have not yet formed a virtuous circle of coordinated development. Therefore, how to promote the coordinated development of innovation input and output is the key to achieving the goal of the rise of China’s MBI. Therefore, the research on the internal coupling coordination of the technological innovation system (TIS) in China’s MBI may have great theoretical and practical significance for improving the overall development level of industrial innovation.

As a strategic emerging marine industry, the MBI has not been studied systematically so far. Previous studies have mainly involved, for example, the influencing factors of industrial development (Calado et al., 2018; Fu et al., 2018), factor allocation and its mechanism (Dai et al., 2017; Fu et al., 2018), industrial development path and model (Bianchi et al., 2011; Huang and Zhou, 2015; Fu et al., 2020). It has been recognized that technology plays a decisive role in the MBI, which is reflected in the academic discussion of the development trend of basic research competitiveness (Zhang and Meng, 2019), the international cooperation mechanisms of industrialization (Fu et al., 2015), and the industry-university-research cooperation models (Zhang and Long, 2019). In general, in terms of research content, studies have involved technological innovation in the MBI mainly with qualitative analysis method, focusing on the development path optimization of the innovation chain. However, up to date, the quantitative research was insufficient on the relationship between the input and output factors of industrial technological innovation. Previous works have not solved the problems of the coordinated development of industrial innovation input and output. From the internal perspective, more attention should be paid to the coordinated development of subsystems.

The methods to explore the relationship between input and output of industrial innovation in other fields could be referenced to the MBI. Previous studies mainly focused on the evaluation of efficiency and performance to reflect the one-way effect of innovation input on output by using the methods of stochastic frontier approach (SFA), data envelopment analysis (DEA) (Chen et al., 2018; Jie et al., 2020; Lin and Luan, 2020), and regression analysis (Pan and Fan, 2008). The correlation or causality between the indicators of the innovation input subsystem and output subsystem was explored mainly using multivariate statistical analysis methods including the gray correlation method (Zhang, 2013), Pearson correlation method (Zhang and Wang, 2008) and typical correlation method (Huang et al., 2017), and quantitative analysis methods such as Granger causality test (Wei et al., 2014). However, these methods ignored the coordination between innovation input and output subsystems. It should be noted that the coupling coordination model has been proved to be an effective method to articulate the strength and excellence of the two-way interaction relationship across different systems, so as to be widely used in the studies of system relationships in different fields (Zhang et al., 2017; Jiao et al., 2019).

In the present study, the time-series development regularities of the coupling coordination of TIS in China’s MBI were empirically analyzed with the capacity coupling coordination model. The interaction and coordination between the innovation input and output subsystems of the MBI in China from 2008 to 2018 were explored, and the obstacle factors that restrict the coupling coordination level of TIS were identified through the obstacle model to improve the innovative development of MBI in China.

2 Theoretical Analysis of the Coupling Mechanism of TIS in China’s MBI

The running status of TIS in the MBI of China was investigated in the marine biopharmaceutical-related organizations, including enterprises, universities, government departments and medical consulting agencies, from the perspectives of innovation input and output. On this basis, a coupling mechanism diagram of TIS in the MBI was constructed based on innovation system theory, industry chain theory, production factor theory and coupling theory, as shown in Fig.1.

In the MBI, the innovation system is comprehensive, in which the innovation input and innovation output display a significant coupling characteristic. There are diverse, non-linear and dynamic interactions in the system, in which every link and factor interacts and organically combines with each other to form the whole innovation system (Shan and Su, 2011). According to the transfor-
The innovation process of innovation achievements, the innovation system could be divided into innovation input subsystem and innovation output subsystem. The innovation input includes fund input, personnel input and project input, among which project input could provide the important channel support for fund and personnel resources. The innovation output is composed of innovative knowledge output and innovation economic benefits output. There is an interactive relationship between these two subsystems.

Innovation input, represented by resource base, is the necessary condition to achieve industrial innovation output. The MBI innovation chain could be divided into four main links, including marine drug candidate discovery, drug development, manufacturing, consumption and circulation links (Fig.1). Every link is a process from innovation input to innovation output. Sufficient innovation input and reasonable structure configuration in each link play a vital role in promoting the formation of innovation output (Frank et al., 2016). Specifically, in the R&D link, the core of the innovation chain, the academic papers derived from the research on marine biochemistry, pharmacology and clinical medicine may be published under the joint actions of fund input and personnel input in the links of basic research, application research, and test and development (T&D). Patents could also be created from the new chemical entity, bioactive composition, and medical use. All of these achievements belong to innovative knowledge output. In the links of manufacturing, consumption and circulation, the innovative achievements could be transformed into products to promote the industrialization of innovative drugs, and the market economic benefits may be realized, through the input of application projects, funds, and talents.

The improvement of the innovation output level has positive feedback effects on the innovation input. The quality and transformation efficiency of innovative knowledge output, such as papers and patents, are related to innovation economic benefits output. As a material guarantee for the continuous innovation resources input, the capital gains of innovation economic benefits output have become a key part of the continuous cycle of the innovation system. For example, marine biopharmaceutical research institutions (MBRIs) may, as a marketing license holder, entrust a pharmaceutical company to produce and obtain sales revenue. After obtaining market returns from the company, the institution continues to increase R&D investment to promote the continuous transformation of scientific research achievements. According to the level of industrial added value, the government provides differentiated policy support for follow-up innovation activities, which, in turn, affects the investment scale of innovation factors such as projects, funds and personnel. Another feedback effect is the superimposed effect of innovation ability. Under the effect of a positive feedback mechanism within an innovation system, the improvement of an innovation output subsystem may enhance the innovation capability of the whole system and promote the expansion of innovation input scale and the rational allocation of the input structure, so as to improve the innovation output efficiency.

From the above analysis, it could be deduced that only through the coordinated development of the innovation input and innovation output subsystems in the MBI can the innovation system shift to an optimal cycle of interactions with a synergistic effect. If the innovation input is insufficient or the industrial innovation capability is low, the innovation input resources will not be able to achieve highly efficient allocation, and consequently restrict the development of the innovation output subsystem.
the material support effect of the positive feedback mechanism on the innovation input subsystem will be hindered, leading to the malfunction of the innovation system, and ultimately disturbing the orderly operation of the MBI innovation system and the improvement of the overall development level of the industry.

3 Empirical Analysis on the Coupling Coordination of TIS in China’s MBI

Based on the above analysis of the coupling mechanism of TIS in the MBI, the regularities of time-series development and change of the MBI in China from 2008 to 2018 were empirically analyzed with the capacity coupling coordination model. Then, the obstacle factors that restrict the coupling coordination level of TIS were identified through the obstacle model.

3.1 Measurement Models, Indicators and Data Description

3.1.1 Measurement models

(1) Evaluation models of comprehensive development level

Before evaluating the level of coupling coordination of TIS in the MBI, the comprehensive development level of each subsystem was measured with the linear weighting method. The calculation formula is as follows:

\[ U_t = \sum_{j=1}^{m} X_{1j} \lambda_{1j} , \quad U_{2t} = \sum_{j=1}^{m} X_{2j} \lambda_{2j} . \]  

(1)

In the formula, \( U_t \) and \( U_{2t} \) represent the comprehensive development level index of innovation input subsystem and innovation output subsystem of MBI in year \( t \), respectively; \( X_{1j} \) and \( X_{2j} \) represent the contribution of each indicator to the innovation input subsystem and innovation output subsystem, respectively; \( \lambda_{1j} \) and \( \lambda_{2j} \) are the weight values of the indicators of the two subsystems, obtained by objective weighting with the entropy weight method. To eliminate the measurement result deviation caused by the differences in original data dimensions and attributes, each indicator’s data were standardized with the maximum difference normalization method. The calculation formula is as follows:

Positive indicator: \( X'_y = \frac{X_y - \min(X_y)}{\max(X_y) - \min(X_y)} \).

Negative indicator: \( X'_y = \frac{\max(X_y) - X_y}{\max(X_y) - \min(X_y)} \).  

(2)

Since the zero value may appear after the standardization of the minimum values of the original data, the subsequent weight assignment will be meaningless. Therefore, the data of each indicator is nonnegatively processed with formula (3) to finally obtain the efficacy of each indicator.

\[ X_y = X'_y \times 0.99 + 0.01. \]  

(3)

(2) Coupling correlation degree and coupling coordination degree models

Based on the capacity coupling model in physics, a coupling correlation model of the binary subsystems of innovation input-output in the MBI was established. The calculation formula is as follows:

\[ C_t = F(U_{1t}, U_{2t}) = \frac{U_t(U_{1t}U_{2t}^eta + 1)}{U_{1t} + U_{2t}^{-eta}} , \]  

(4)

\( C_t \) represents the degree of coupling correlation between innovation input and innovation output. \( C_t \in [0,1] \) entails that the larger the \( C_t \) value is, the higher the degree of coupling, and the better the synergy effect is. Since the degree of coupling correlation only reflects the strength of the interaction between the subsystems, it cannot show whether the degree of coordination is good or bad, which may create an illusion of a high coupling degree when the comprehensive development level index of the subsystems is low. Therefore, it is necessary to introduce an additional coupling coordination degree model that is more objective and scientific. The calculation formula is as follows:

\[ D_t = (C_t \times U_t)^{\frac{1}{2}} , \]  

(5)

\[ U_t = \alpha \times U_{1t} + \beta \times U_{2t} . \]  

(6)

\( D_t \) and \( U_t \) are the coupling coordination degree and the comprehensive coordination index of the TIS in year \( t \) of the MBI, respectively. \( \alpha \) and \( \beta \) are the relative importance of the two subsystems in the comprehensive coordination index. This paper defines \( \alpha = \beta = 0.5 \), which means that both provide equally important contributions to the innovation activities of the MBI. In addition, referring to the related research, the degree of coupling coordination \( D \) is classified and shown in Table 1 (Wang and Wang, 2020).

| Coupling coordination degree \( D \) | Classification | Type subdivision of coupling coordination |
|-------------------------------------|----------------|----------------------------------------|
| 0.00 – 0.20 | Serious disordered | \( U_1 > U_2 \), Lagging output of innovation |
| 0.20 – 0.40 | Moderate disordered | \( U_1 = U_2 \), Simultaneous development of innovation input and output |
| 0.40 – 0.50 | Mild disordered | \( U_1 < U_2 \), Lagging input of innovation |
| 0.50 – 0.70 | Primary coordinated | |
| 0.70 – 0.90 | Well-coordinated | |
| 0.90 – 1.00 | High-quality coordinated | |

3.3 Obstacle model

To further clarify the improvement direction of the coordinated development of TIS in the MBI, the obstacle model was applied to identify the obstacle factors. The
calculation formula is as follows:

\[ F_j = R_j \lambda_j, \quad (7) \]

\[ H_j = \frac{F_j (1 - X_j)}{\sum_{i=1}^{n} F_i (1 - X_i)} \times 100\%. \quad (8) \]

\( F_j \) represents the contribution degree of the factor \( j \). \( R_j \) represents the weight value of subsystem \( i \). \( \lambda_j \) represents the weight value of factor \( j \) in the subsystem. In addition, the entropy method was adopted for weighting. \( X_j \) represents the standardized value of the factor \( j \), and \( H_j \) represents the obstacle degree of the factor \( j \). The larger the \( H_j \) is, the higher the obstacle degree of the factor \( j \) blocking the coordinated development of innovation input and innovation output in the MBI.

### 3.1.2 Indicator source and data description

#### (1) Indicator system construction

To more scientifically and accurately measure the coupling coordination level of TIS, based on the analysis of the coupling mechanism, a coupling coordination evaluation indicator system of innovation input and innovation output of China’s MBI was constructed according to the principles of systematicity, feasibility and simplicity.

The innovation input subsystem includes three primary indicators: innovation fund input, innovation labor input, and innovation scale input. The selection of input indicators should reflect the fund input level of the industry in R&D, R&D achievement application and other links as well as the characteristics of current government funding dominance in China’s MBI (Fu et al., 2015). The two innovation fund input indicators were selected as the stock of R&D expenditures of the MBRIs and the government funding allocated by the ‘China Torch Program’ to the field of biological and medical technology. Innovation labor input includes R&D personnel and the technology activity personnel of the MBRIs, reflecting the level of personnel input into R&D, industrialization, auxiliary technology services and other links (Shao et al., 2016). Technology projects are the basic forms of technological innovation activities (Ye et al., 2012). Therefore, the Chinese government’s policy support for innovation activities in a certain field could also be implemented with project input. Thus, this study selected the numbers of all technology projects in the MBI and the R&D projects among them to represent the level of industrial innovation scale input, reflecting the basic scale of industrial innovation activities and the orientation of government policy support.

The innovation output subsystem includes two primary indicators: innovative knowledge output and innovation economic benefits output. The previous research has generally used patents to measure innovative knowledge output. In view of the advantages and disadvantages to measure the output level by using the patent application or patent licensing only (Zheng and Ding, 2007), this study comprehensively selected the number of patent applications and the number of patent licenses to reflect the activity levels of knowledge innovation efforts and market competitiveness and potential of innovative knowledge output, respectively. In recent years, the publication of academic papers has become an important indicator for exploring the level of basic research activities in many fields (Zhang et al., 2016). Therefore, the present study also selected the academic papers in the marine biopharmaceutical field collected from Science Citation Index Expanded (SCI-E) as an indicator to reflect the innovative knowledge output. The papers collected in this database were of relatively high quality, which may reflect the research trend of the field during a certain period of time. Generally, product sales revenue or product output value reflects the indirect innovation benefits output obtained through the incremental innovation of process and technology, while the new product sales revenue reflects the direct innovation economic benefits output (Zheng and Ding, 2007). All of product output value, product sales revenue and new product sales revenue could reflect the industrial added value which is a referring indicator of government policy support. Policy support is an important factor that has affected the development of MBI. Hence, the industrial added value was chosen as an indicator to measure the innovation economic benefits output of the MBI. Based on the above analysis, an evaluation indicator system was constructed, as shown in Table 2.

#### (2) Data description

The data of the indicators used in this paper, including...

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**Table 2 Evaluation indicator system of coupling coordination of innovation input subsystem and innovation output subsystem in China’s MBI**

| Subsystem                        | Primary indicator | Secondary indicator | Indicator attribute | Weight |
|----------------------------------|-------------------|---------------------|---------------------|--------|
| Innovation fund input           | \( a_1 \)         | Stock of R&D expenditures of MBRIs \( a_{i1} \) | +                   | 0.1527 |
| Innovation labor input          | \( a_2 \)         | Government funding \( a_{i2} \)               | +                   | 0.1146 |
| Innovation scale input          | \( a_3 \)         | R&D personnel of MBRIs \( a_{i3} \)           | +                   | 0.1507 |
| Innovation knowledge output     | \( b_1 \)         | Technology activity personnel of MBRIs \( a_{i2} \) | +                   | 0.1184 |
| Innovation economic benefits output | \( b_2 \) | Number of industrial R&D projects \( a_{i1} \) | +                   | 0.1940 |
|                                  |                   | Number of industrial technology projects \( a_{i2} \) | +                   | 0.2696 |
|                                  |                   | Number of patent applications \( b_{i1} \)    | +                   | 0.2382 |
|                                  |                   | Number of patent licensing \( b_{i2} \)      | +                   | 0.2623 |
|                                  |                   | Number of papers collected in SCI-E \( b_{i3} \) | +                  | 0.2133 |
|                                  |                   | Industrial added value \( b_{i1} \)          | +                   | 0.2862 |

Notes: The data in brackets are the weight values, obtained by objective weighting with the entropy weight method.
innovation labor input, innovation scale input, and innovation economic benefits output, were from the China Marine Statistical Yearbook. Innovative knowledge output data were retrieval data, among which the data of the patent application and patent licensing indicators were from the Patent Star Search System, and the data of paper indicator from SCI-E, obtained by referring to the authoritative keywords concerning the marine biopharmaceutical field (Zhang and Meng, 2019). For the innovation fund input indicator, the government funding data were from the China Statistical Yearbook on Science and Technology. Because innovation is a continuous process, the key function of R&D funding is in its accumulation which cannot be reflected by the flow indicator of R&D expenditure. Therefore, the R&D expenditure stock data were obtained by converting the R&D expenditure flow data with the perpetual inventory method. The R&D expenditure flow data were from the China Marine Statistics Yearbook. The calculation formula is as follows:

\[ RD_t = (1 - \delta_t)RD_{t-1} + E_t. \] (9)

\( RD_t \) and \( RD_{t-1} \) indicate the stock of R&D expenditures in periods \( t \) and \( t-1 \). \( E_t \) is the stock of R&D expenditures at constant prices. The price index was obtained by processing the weighted average of the fixed asset price index and consumer price index obtained from the China Statistical Yearbook. With reference to the research on R&D capital (Zhu and Xu, 2003), the weights of the fixed asset price index and consumer price index were set to 55% and 45%, respectively. Based on experience (Hu et al., 2005), the depreciation rate \( \delta_t \) was set at 15%. The base period R&D expenditure stock data of the MBI were determined by dividing the base period flow data by the sum of the depreciation rate and the average annual growth rate. The average annual growth rate was calculated by the geometric average method.

Since the publication of the China Marine Statistical Yearbook was up to 2017, only the relevant data from 2008–2016 were obtained. The 2017–2018 data were obtained through extrapolated forecasting with the selected appropriate smoothing coefficients by the exponential smoothing method. In the process of extrapolated forecasting, different smoothing coefficients were used for trial evaluation with the exponential smoothing model. By comparing the mean absolute percentage error in each trial evaluation result, the smoothing coefficients with the minimum error were selected as the prediction coefficients.

3.2 Empirical Analysis Results

3.2.1 Analysis of the comprehensive development level indexes of innovation input subsystem and innovation output subsystem in China’s MBI

Based on the comprehensive development level evaluation model, the comprehensive development level indexes were calculated for the innovation input and output subsystems of China’s MBI from 2008 to 2018.

It could be found that the comprehensive index of industrial innovation output subsystem maintained a growing trend from 2008 to 2018 in China, as shown in Fig.2.

The MBI has been considered as an emerging industry that is still in the rapid growth stage of the technology life cycle (Li and Wang, 2017). Correspondingly, the academic paper output has continued to rise in the basic research of MBI (Zhang and Meng, 2019). Patent output also showed strong vitality of technological innovation in the study fields of cardio-cerebrovascular and anti-infection marine drugs. It should be noted that even though the number of bioactive compounds discovered from the sea reached an average of 200–300 per year, only few compounds with authorized patents have truly become drug candidates to enter the stage of technological achievement transformation (Verónica et al., 2017; Zhang et al., 2018). Moreover, the awareness of reasonable distribution of new patents especially core patents in the innovation
chain was relatively weak (Xu and Zhu, 2020). Specifically, there was an obvious lack of the R&D for new, original, and innovative marine drugs with real clinical values in response to the need for prevention and control of current human disease spectrum. It should be pointed out that the current high proportion of industrial added value mainly came from low value-added products, such as marine biopharmaceutical active ingredients, which have a low level of technology and insufficient marketing competitiveness with a low pulling effect on the added value of the MBI (Prospective Industry Research Institute, 2017). This situation was in accordance with the status of the ‘high-end industry, low-end technology’ development model of China’s MBI, which featured as weak market competitiveness of innovative knowledge output and a low rate of technological achievement industrialization.

It could be seen that the comprehensive index of industrial innovation input subsystem fluctuated at a low level from 2008 to 2018 (Fig.2). Among the input indicators, industrial technology projects related to the MBI were not only insufficiently invested but also unstable. The fluctuation of the standardized value was in the range of 0–0.5, and the fluctuation trend was exactly the same as that of the comprehensive index of industrial innovation input, as shown in Fig.3.

Fig.3 The development level of technology projects and innovation input subsystem in China’s MBI.

Based on the original statistical data, the instability of the number of industrial technology projects led to the fluctuation response of indicators such as R&D expenditures and technology activity personnel, and subsequently caused the volatility of the overall innovation input subsystem. From the perspective of the input transmission mechanism, there was no continuous and effective mechanism for professional talents training or special management mechanism for scientific research funding guarantee, and consequently led to instability innovation input support for industrial innovation-driven development, resulting in the instability of the innovation input subsystem. In fact, in the current MBI of China, a technology policy support system was not complete yet, which should play the support role to innovation input subsystem in the operation of industrial innovation system. Consequently, there was also a lack of a stable fund input and talent input mechanism with a systematic and continuous funding model for technology projects.

3.2.2 Analysis of the coupling coordination level of TIS in China’s MBI

On the basis of measuring the two comprehensive indexes of the innovation input subsystem and innovation output subsystem of China’s MBI, the coupling correlation degree and coupling coordination degree between the two subsystems were evaluated. As shown in Table 3, the coupling coordination level of TIS in China’s MBI changed from mild disordered into well-coordinated from 2008 to 2018. However, due to the instability of the innovation input subsystem, the coupling coordination level showed a fluctuation situation of alternating rises and falls. On the whole, the development type of the innovation system changed from a lagging output of innovation into a lagging input of innovation.

The coupling coordination degree could be divided into three stages: the mild disordered period, the primary coordinated period, and the well-coordinated development period. The first stage of coupling coordination of TIS was from 2008 to 2009 characterized as mild disordered, in which the allocation of innovation resources was in a state of low efficiency, and the level of innovation output was also low. Fortunately, in this stage, a good policy environment was created for the basic research of marine drugs. Active policy support for later industrial innovation was provided by government departments. The ‘Na-
nitional Major Scientific and Technological Special Project for Significant New Drugs Development (2008–2020)\textsuperscript{1}, issued in 2008, was the largest and most invested technology plan for innovative drugs since the founding of new China. In this stage, the basic research related to marine drugs received unprecedented attention and harvested a series of exploratory, basic and paving achievements. One of the prominent examples was the publication of ‘Chinese Marine Materia Medica’ in 2009 (Guan and Wang, 2009), which is China’s first large-scale marine drug classic, providing a strong theoretical support for R&D of marine drugs with detailed and accurate literature. These efforts laid a solid foundation for promoting the technological innovation of MBI. It is worth noting that, although the degree of coupling coordination at this stage was mild disordered, with the support of active policies, the R&D projects and technology projects of MBI reached the highest level in 2009. The increase of the innovation scale also improved the levels of innovation input indicators, such as greatly improved the input of technology activity personnel, ultimately leading to the highest level of the comprehensive index of innovation input. However, due to the hysteresis effect of the innovation input, the level of innovation output was low, thus the TIS remained in a relatively low-level coordination state in 2009.

Table 3 Coupling coordination level of TIS in China’s MBI

| Year   | Coupling correlation degree $C$ | Coupling coordination degree $D$ | Coupling coordination level          | Subdivision of coupling coordination          |
|--------|---------------------------------|---------------------------------|--------------------------------------|----------------------------------------------|
| 2008   | 0.8899                          | 0.4524                          | Mild disordered                     | Lagging output of innovation                  |
| 2009   | 0.6402                          | 0.4898                          | Mild disordered                     | Lagging output of innovation                  |
| 2010   | 0.8067                          | 0.5684                          | Primary coordinated                 | Lagging output of innovation                  |
| 2011   | 0.9654                          | 0.6011                          | Primary coordinated                 | Lagging output of innovation                  |
| 2012   | 0.9231                          | 0.5026                          | Primary coordinated                 | Lagging input of innovation                   |
| 2013   | 0.9781                          | 0.6082                          | Primary coordinated                 | Lagging input of innovation                   |
| 2014   | 0.9487                          | 0.5988                          | Primary coordinated                 | Lagging input of innovation                   |
| 2015   | 0.9987                          | 0.7046                          | Well-coordinated                    | Lagging input of innovation                   |
| 2016   | 0.9984                          | 0.7058                          | Well-coordinated                    | Lagging input of innovation                   |
| 2017   | 0.9604                          | 0.8203                          | Well-coordinated                    | Lagging input of innovation                   |
| 2018   | 0.9542                          | 0.8544                          | Well-coordinated                    | Lagging input of innovation                   |

The second stage was the primary coordinated period from 2010 to 2014. The innovation output achieved a state of steady growth, while the instability of the innovation input subsystem led to a fluctuating upward trend in the coordinated development level. The supporting effect of the early-stage innovation input on the innovation output began to appear at this stage, as demonstrated by the increase of comprehensive output index from 0.1251 in 2008 to 0.4974 in 2014. However, the numbers of industrial R&D projects and technology projects were significantly reduced at this stage, and the comprehensive index of innovation input was a downward trend and fluctuated greatly.

The third stage was the period of well-coordinated development from 2015 to 2018. Owing to the high level of the comprehensive index of the innovation input and output subsystems, the interaction promotion effect between these two subsystems showed an effective state of coordination. During this period, the MBI development received unprecedented attention. For the first time, the plan and objectives for the MBI development were put forward in China’s Five-Year Plan, such as ‘the 13th Five-Year Plan for Biological Industry Development in China (2016)’ and ‘the 13th Five-Year Special Plan for Technological Innovation in the Marine Field in China (2017)’. It was greatly supported to create innovative products with independent intellectual property rights and broad market prospects, including marine drugs and marine bio-products with green, safe and efficient functions. It should be emphasized that the Chinese ‘Blue Drugs Bank’ development plan was launched in 2016, which aimed to innovatively research and systematically develop marine drugs targeting the major diseases that seriously endanger human health. Following the expert demonstration of new marine drug creation, a pre-research project was officially implemented in 2017 and then upgraded to a national strategy in 2018. With the support of these strategic policies, high-level R&D talents concentrating on innovative marine drugs began to be gathered in the MBI, and many pharmaceutical companies and venture capital firms turned their attention to the MBI. Consequently, the support for industrial innovation factors was significantly enhanced. As a result, the comprehensive index of innovation input continued to increase (Fig.2). At the same time, the allocation structure of innovative resources was continuously improved, and the innovation output was more efficient, resulting in the continual emerging of innovation achievements. One of the remarkable achievements was represented by the original innovative marine drug GV-971 that was completed its phase III clinical trial in 2018 and subsequently approved for marketing in the next year. A batch of new original candidate marine drugs and innovative medical products represented by BG316 and TGC161 were developed in an orderly manner. A series of marine-derived functional products, such as specialized medical food, health food, and cosmetics, were on the market one after another, further promoting the formation of a high-end industrial chain in the MBI. As a result, the comprehensive index of innovation output was markedly increased.

As to the development type of the TIS in China’s MBI, it shifted from lagging output of innovation to lagging input of innovation from 2008 to 2018. The level of innovation output in 2008–2011 lagged behind innovation.
input, while innovation input in 2012–2018 lagged behind innovation output (Table 3). It was indicated that innovation input had a significant driving effect on the improvement of the output level in the MBI. However, as a high-input industry, the development of MBI in China has been limited by the insufficient industrial innovation input, which could not further play a key supporting role in the scale and quality of innovation output. In summary, although many achievements were obtained in the basic research phase of the industry innovation chain, the MBI still faced ongoing problems, especially the difficulties in the industrialization of technological research achievements.

3.2.3 Identifying obstacles to the coordinated development of TIS in China’s MBI

To further improve the coupling coordination level of TIS in China’s MBI, the obstacle degrees of various factors in the innovation input subsystem and output subsystem were calculated with the obstacle model. Then, the factors that restrict the coordinated development of the subsystems were identified.

After calculation, the obstacle degrees of primary indicators were drawn with Origin8.6 software, as shown in Fig.4. It was displayed that the obstacle degrees of primary indicators innovation scale input, innovation fund input, innovation labor input, innovation economic benefits output, and innovative knowledge output were 21.59%, 8.69%, 8.14%, 6.25%, and 5.64%, respectively (Fig.4). Among these five primary indicators, the first three belonged to the industrial innovation input subsystem, indicating that insufficient innovation input was the main factor restricting the coordinated development of TIS in the MBI.

![Fig.4 The obstacle degrees of the primary indicators for the coordinated development of TIS in China’s MBI.](image)

(1) Innovation scale input

Innovation scale input plays a fundamental role in the innovation system, directly affecting the input level of innovation resources and further affecting the innovation output and even the operating efficiency of the entire innovation system. The policy support for technological innovation in the MBI could be reflected in the innovation scale input indicator, represented by the number of industrial technology projects. The MBI in China has been classified as a part of the biological industry or an emerging marine industry with strategic importance. It is undeniable that a stable and effective innovation policy support system has not yet been formed in China. Although a series of policies to support innovative industrial development have been issued in China, there are no special plans and implementation rules promulgated for the MBI’s development. This led to the lack of systematicness, continuity and pertinence of the industrial innovation scale input. Macro planning lacked specific implementation policies, which affected the effective allocation of specific innovation factors.

(2) Innovation fund input

The MBI has typical capital-intensive characteristics. Each link in the new drug creation chain requires continuous and large-scale funding support. Although China has provided significant funding support for R&D pro-
projects in MBI, there is still a large funding gap compared with that in American-European developed countries (Prospective Industry Research Institute, 2017). In the United States, more than one hundred million dollars a year have been funded for the R&D of marine drugs by the National Research Council of the United States and the United States National Cancer Institute. While the Marine Biotechnology Research Institute and Marine Science and Technology Center of Japan spent approximately one hundred million dollars a year on the R&D of marine drugs. In terms of a funding support structure in China, the MBI mainly relies on government funding, such as the ‘863’ Program, the ‘973’ Program, the ‘National Natural Science Foundation of China’, and the ‘Key R&D Special Program for New Drugs’. The monotonicity of funding subjects also restricted the expansion of the funding scale of China’s MBI.

(3) Innovation labor input

Talented personnel are the main body of technology research and innovation activities. Each link in the new drug creation chain requires the support of high-level professional talents. As the core of talent training organizations, universities and research institutions are two important sources of technology research talents. At present, there are few universities in China that have formed a complete pharmacy talent training system featuring marine drug research. As a result, an integrated marine biopharmaceutical talent supply system has not been formed yet, which made it difficult to meet the demand for constructing a professional team of scientific research and innovation. In addition, the transformation of scientific research achievements requires a complete talent allocation system. Both research talents and development talents, engaged in basic scientific research and original technological inventions, are important productive forces in the R&D of new drugs. Talents with application-skill and talents for sales and marketing guarantee the implementation of production, merchandise sales and brand promotion. In the process of innovation, the role of technology service personnel in supporting activities, such as marine biotechnology promotion and drug evaluation, should not be ignored. However, in recent years, the scale of technology service personnel was still small in China’s MBI (Prospective Industry Research Institute, 2017). High-level researchers of marine biomedicine not only engaged in scientific research but also have to serve themselves, which affected the efficiency of innovation output.

In order to explore the main obstacle factors blocking the coupling coordination of TIS in China’s MBI, the obstacle degrees of the secondary indicators were calculated. It could be found that the average obstacle degrees of the secondary indicators ranged from 5.16% to 26.14%. Among them, the average obstacle degrees of technology projects, R&D projects, and R&D expenditures were higher than 10% (Table 4), displaying greater constraints on the coordinated development of TIS in the MBI.

Table 4 The obstacle degrees of secondary indicators for the coordinated development of TIS in China’s MBI

| Obstacle degree (%) | a1 | a2 | a3 | a4 | a5 | b1 | b2 | b3 | b4 |
|---------------------|----|----|----|----|----|----|----|----|----|
| 2008                | 16.07 | 10.89 | 11.25 | 12.46 | 7.85 | 12.16 | 5.27 | 8.70 | 5.97 |
| 2009                | 22.72 | 18.14 | 13.08 | 0.00 | 0.00 | 0.00 | 11.59 | 9.52 | 10.65 |
| 2010                | 21.50 | 13.74 | 13.05 | 0.00 | 3.54 | 6.08 | 11.87 | 11.88 | 5.32 |
| 2011                | 14.21 | 8.17 | 5.73 | 4.90 | 14.65 | 22.18 | 7.31 | 7.63 | 6.61 |
| 2012                | 9.68 | 11 | 11.71 | 10.21 | 17.25 | 25.98 | 3.71 | 4.35 | 5.47 |
| 2013                | 11.22 | 2.23 | 17.11 | 4.96 | 20.33 | 24.49 | 5.03 | 5.55 | 4.06 |
| 2014                | 10.97 | 2.12 | 16.57 | 3.43 | 21.33 | 27.96 | 4.66 | 3.31 | 5.32 |
| 2015                | 11.48 | 1.18 | 3.54 | 15.00 | 16.32 | 30.32 | 3.37 | 7.67 | 6.74 |
| 2016                | 6.31 | 0.00 | 0.00 | 7.28 | 25.05 | 39.35 | 3.94 | 10.43 | 4.91 |
| 2017                | 3.57 | 0.40 | 1.82 | 11.70 | 29.41 | 46.87 | 0.00 | 0.00 | 4.74 |
| 2018                | 0.00 | 0.45 | 2.07 | 13.25 | 31.71 | 52.12 | 0.00 | 0.40 | 0.00 |
| Mean                | 11.61 | 5.77 | 8.72 | 7.56 | 17.04 | 26.14 | 5.16 | 6.31 | 5.44 |

Notes: The specific meanings of ai and bj have shown in Table 2.

The number of technology projects that belong to the innovation scale input was found to be the primary obstacle factor to the coordinated development of TIS in the MBI of China. As the carrier of R&D resources input, the number of technology projects could directly affect the innovation output. In recent years, the number and supporting intensity of the technology projects in the MBI were relatively low. Consequently, the R&D projects and R&D expenditures of the R&D link in the innovation input subsystem showed a relatively high obstacle degree (Table 4), which seriously restricted the innovation-driven development of the industry. It was indicated that the link of new drugs R&D, as a core of the innovation chain, has greater improvement space. At present, the basic research of marine biomedicine in China occupies a place in the world, and especially the research on marine natural product chemistry has been at the forefront of the world. However, as the efficient coordination mechanism for the integration of industry-university-research has not been established in the MBI yet, the low efficiency of the transformation of scientific research achievements has become the biggest problem in the MBI of China.

In the discovery stage of marine drugs, the achievements of basic research have the property of ‘public goods’. The government should play a dominant role in the field of resources input during this stage, and the enterprises could obtain basic research achievements through the diffusion of knowledge or technology via ‘free-riding’ behavior. However, in this way, it would be difficult for the enterprises to fully understand and effec-
tively absorb the market values contained in the basic research achievements, restricting the subsequent transformation of scientific research achievements and industrialization (Zhang and Meng, 2019). Consequently, it would be difficult to achieve simultaneous improvement in the industry’s core technical capabilities with basic research.

The above analysis indicated that the subjects of resources input were monotonic in the R&D process of TIS in the MBI of China, which limited the scale of resources input. At the same time, the unreasonable allocation of innovation resources input weakened the key supporting role of basic research for the R&D of new drugs, blocking the optimal cycle of TIS in the MBI.

4 Conclusions and Policy Recommendations

4.1 Conclusions

An evaluation indicator system of innovation input-output coupling coordination was constructed based on the analysis of the coupling coordination mechanism of TIS in the MBI of China. The level of coupling coordination development between the technological innovation input-output subsystems was empirically calculated with the capacity coupling coordination model. The obstacle factors to the coupling coordination development of TIS were further identified via the obstacle model. It was found that the development type of the TIS has changed from a lagging output of innovation into a lagging input of innovation in China from 2008 to 2018, with the comprehensive index of innovation input fluctuating at a low level. The innovation output index basically maintained a growing trend, but the development quality needed to be improved. The coupling coordination level exhibited obvious fluctuation characteristics, although the coupling coordination grade displayed an upward development trend. The coupling coordination level of TIS has undergone an adjustment process from mild disordered to primary coordinated, and further to well-coordinated with a fluctuating level of coupling coordination caused by the instability of the innovation input subsystem. Insufficient innovation input restricted the coordinated development of the various factors of TIS. Among the obstacle factors of innovation input, the top three obstacle factors, including technology projects, R&D projects and R&D expenditures, were recognized.

4.2 Policy Recommendations

Based on the above analysis, focusing on the problems of insufficient innovation input and poor quality of output in TIS, the suggestions were proposed to improve the coupling coordination level of TIS in the MBI of China.

(1) Improving policy support to increase the scale input of innovation input subsystem

In view of the insufficient policy support, it was suggested to improve the intensity and accuracy of the government’s industrial policy support and increase the investment in innovation scale. A special policy support for the MBI could be strengthened and articulated to form a stable and integrated industrial technology policy support system. In this way, the macro planning could be better implemented in all links of the industry from the utilization of marine bioresources to the industrialization of scientific research achievements. At present, the ‘Blue Drugs Bank’ development plan implemented in Qingdao, China has achieved remarkable achievements. Drawing on existing experience, a national ‘Blue Drugs Bank’ development plan should be implemented through gradually including all the coastal provinces and cities in the scope of policy support system and building other pilot cities of the ‘Blue Drugs Bank’ development for the purpose of finally constructing the special policy support system of MBI. The government should play a leading role with policy and reduce the threshold for the innovative R&D of enterprises through policy support, such as tax reduction and exemption. In turn, these measures may attract domestic large-scale marine biopharmaceutical companies with strong scientific research capabilities to participate in the R&D process, improving the scale of R&D funding and R&D competitiveness.

(2) Establishing a multichannel funding guarantee mechanism to increase the fund input of innovation input subsystem

It is necessary to establish a funding system for technology projects led by the government with the participation of industry departments, enterprises and other subjects. With the multiple funding subjects, the transformation process of scientific research achievements could be speeded up through increasing the support for R&D projects and achievement application projects. Different special fundings are proposed for key innovation nodes such as personnel training, drug discovery and achievement transformation. In particular, it is necessary to establish an information-sharing platform for funding operation, with which the transparency, standardization and normalized supervision of the operation of special funding could be realized. It is also necessary to broaden the financing channels by adopting tendentious policies to encourage national social funding to enter the MBI field, and attract foreign government funding, foreign enterprise funding and other international funding into key innovation links. It could be expected that a multi-subjects funding system, led by the government with the participation of enterprises, financing institutions and crowd-funding, may promote the industrialization and marketization of all scientific research achievements.

(3) Establishing a professional technical talent system to increase the innovation labor input of innovation input subsystem

In view of the shortage of high-level talents, a system for the introduction and training of professional technical talents should be established to play the basic supporting role to meet the demand for high-tech development of MBI. Guided by market demand, a complete pharmaceutical personnel training system should be formed through...
education programs to cultivate high-level professionals, such as undergraduate-master’s-doctoral degrees program on marine biopharmaceutics in medicine and pharmacy colleges or universities. It is necessary to strengthen the introduction of high-level talents, and refine the management and assessment policies for talent introduction and local talent protection to prevent brain drain. Specifically, attention should be given to cultivating compound talents who are familiar with the entire process of R&D, production, sales and management to enhance the ability to grasp market demand, transform the achievements of production, sales and management to enhance the ability of talents who are familiar with the entire process of R&D, transformation. On the premise of ensuring the reasonable scale of the core R&D technical team, it should also pay attention to cultivating skilled talents, sales talents, marketing talents and professional service personnel with an appropriate proportion to achieve the optimal allocation of human resources in the industry.

(4) Cultivating the innovation subjects and building innovation platforms.

It is necessary to promote the integrated development of government-industry-university-research-funding-user to improve the quality level of innovation output in the MBI. The academic and research institutions should strengthen the basic research and establish a complete innovation knowledge system in order to make breakthroughs in the field of original, innovative and novel drugs creating based on new targets and new mechanisms. In order to coordinate the balance between the supply and demand of resources and achievements among the MBI’s subjects, it is also necessary to optimize and upgrade the intermediary service agencies represented by the CRO, which may not only play a role in the clinical trial, but also provide a one-stop service for new marine drug creation to meet the major needs of prevention and control for the current diseases. Eventually, it is suggested to establish an industrial technology innovation system with enterprises as the main body, which is a market-oriented and deep integration of industry-university-research. In order to realize the function of the innovation system, it is also necessary to improve the innovation eco-environment that includes government, intermediaries, investment and financing institutions together with other related organizations. Therefore, focusing on the development of the unique medicinal value of marine biological resources, the cooperation among various innovation subjects in key links, such as basic research, achievement transformation and industrialization, should be better promoted to integrate downstream investment and financing needs on the basis of closely combining with the major strategic demands of national new drug creation. Through the high-level coordination and interaction of innovation input and output, the overall development level of the industrial innovation system is prospected to be promoted, truly realizing the innovation-driven, high-quality development of the MBI.

(5) Promoting the discovery of lead compounds and the application of new technologies in multi-fields.

It is necessary to strengthen the research in the field of symbiotic interaction between marine organisms and marine microorganisms or between marine microorganisms, molecular biology and fermentation strategies, and natural combinatorial chemistry. Consequently, more novel and diverse bioactive molecules could be obtained based on the physiological function and ecological function of marine organisms, which can strengthen the supply of source knowledge. Meanwhile, on the basis of maintaining the original complexity and effectiveness of marine natural products, the research and application of common technologies, such as combinatorial chemistry and biosynthesis, should be strengthened to well conduct structural modification for the purpose of meeting the requirements of targets, efficacy, pharmacokinetics and safety. In this way, more lead compounds of marine natural products, which are with important physiological activity and drug prospects, will be developed. Furthermore, it is also necessary to establish marine medicinal bioresources base, marine natural product compound base, target screening and pharmacodynamic verification models and their database, so as to provide a carrier for the strategic reserve of marine medicinal bioresources. In addition, the application of supercomputing virtual technology and high through-put technology in the screening of marine compounds should be promoted to improve the screening efficiency. At the same time, various technologies should be comprehensively utilized to promote the integrated development of basic research and modern development methods.

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