Genome mining of secondary metabolites from a marine-derived
Aspergillus terreus B12

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Received: 19 May 2021 / Revised: 15 August 2021 / Accepted: 19 August 2021 / Published online: 30 August 2021
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Abstract
Owing to the prominent capabilities of bioconversion and biosynthesis, A. terreus has become attractive in biotechnical and pharmaceutical industry. In this work, an Aspergillus strain with potential antibacterial activities, was isolated from sponge in South China Sea. Based on the morphological and phylogenetic analysis, the strain was identified as A. terreus B12. Via the Illumina MiSeq sequencing platform, the complete genome was obtained, showing a genetic richness of biosynthetic gene clusters (BGCs), which might underpin the metabolic plasticity and adaptive resilience for the strain. Genome mining identified 67 BGCs, among which, 6 gene clusters could allocate to known BGCs (100% identity), corresponding to diverse metabolites like clavaric acid, dihydroisoflavipucine/isoflavipucine, dimethylcoprogen, alternariol, aspterric acid, and pyranoigrin E. Moreover, a range of compounds was isolated from B12 fermentation, e.g., terrein, butyrolactone I, terretonin A&E, acoapetaline B, and epi-aszonalenins A. Of note, acoapetaline B and epi-aszonalenins A, which had been respectively reported in plants and A. novofumigatus but with scarce information, was unexpectedly obtained from this species for the first time. The genomic and metabolic heterogeneity observed in strain B12, should be at least partially attributed to the genetic variability and biochemical diversity of A. terreus, which could be an interesting issue open to future efforts.

Keywords Aspergillus terreus · Genome sequence · BGCs · SMs · Marine fungi

Abbreviations
BGCs  Biosynthetic gene clusters
SMs  Secondary metabolites
PDB  Potato Dextrose Broth
MH  Mueller–Hinton
MEA  Malt Extract Agar
MeOH  Methanol; LPCB, lactophenol cotton blue
ITS  Internal transcribed spacer
ML  Maximum-likelihood
GO  Gene Ontology
KEGG  Kyoto Encyclopedia of Genes and Genomes
CAZy  Carbohydrate-Active enZYmes
COG  Clusters of Orthologous Groups
NRPS  Nonribosomal peptide synthase
PKS  Polyketide synthase

Introduction
As a valuable producer of secondary metabolites (SMs), marine fungi represent an underestimated source of biological and chemical diversity, although their distribution and ecological roles often remain obscure. Owing to the particularity of marine environment, many SMs are structurally unique and possess promising biological and pharmacological properties, in comparison with their terrestrial origin counterparts (Rateb and Ebel 2011). For decades, despite the significant increase in the number of structures discovered from marine fungi, the species diversity and the large potential of SMs is not yet adequately represented.

As filter feeders in marine ecosystem, sponges form close associations with diverse groups of microbes, potentially involved in a variety of ecological functions, including SMs generation, which could contribute to an ecological success, to themselves and to the host in niche competition. In our previous work, a range of filamentous fungal strains were isolated from sponges in the South China Sea, typically dominated by Aspergillus and Penicillium sp. (Gao et al. 2020).
Hereon, we present the draft genome of B12, an A. terreus strain with broad antibacterial activities in preliminary screening. Subsequently, genome mining, metabolites separation, and structure determination were performed, partially presenting the biosynthetic potential and chemical diversity of the strain, which highlighted the need for further study and shed some lights on the ecological and biochemical properties of A. terreus strains.

Materials and methods

Strains

Strain B12 was isolated from sponges in a nearby maritime location (17°5’0.70”00 N, 111°31’0.39”00 E). After purification, the strain was inoculated into malt extract agar (MEA, OXOID, UK) with 3% sea salt, 28 °C for 5 days, and then stored for fermentation.

Escherichia coli ATCC 25,922, Klebsiella aerogenes ATCC 700,603, Pseudomonas aeruginosa PA101, methicillin-resistant Staphylococcus aureus (MRSA) USA300, methicillin-resistant Staphylococcus epidermidis (MRSE) ATCC 35,984, Micrococcus luteus ACCC11001, and Acinetobacter baumannii ATCC 19,606 were utilized as control strains. All the above strains were stored in the Marine Pharmaceutical Laboratory of China Pharmaceutical University.

Fermentation for antibacterial screening

The strain B12 was activated in the Potato Dextrose Broth (PDB), then inoculated onto corn medium (corn 1 kg, MgSO4 2 g, sea salt 15 g, malt sugar 20 g, sorbitol 20 g, yeast extract 3 g, tryptophane 0.5 g, sodium glutamate 10 g, K2HPO4 0.5 g, water 1 L) to culture at 28 °C for 15 days. The fermented products were extracted by methanol (MeOH) followed by decompressing distillation to acquire a crude extract. The crude extract was dissolved in 2 mL MeOH for antibacterial activity assay by the agar diffusion method.

The overnight culture of control stains was diluted to OD600nm ≈ 0.1 and spread onto MH agar (Solarbio, China). Wells measuring 6 mm in diameter were punched onto the surface of the agar using a sterile hole puncher. 30 µL crude extract was added to the wells and incubated at 28 °C for 24 h, with standard antibiotics (chloramphenicol, 0.1 mM) as a positive control, and MeOH as a vehicle control. Each assessment was developed in triplicate. The diameters (in mm) of the inhibition zone were recorded to estimate antimicrobial activities, which were expressed by the ratio of the inhibition zone relative to that of the positive control. The bacteriostatic activities were considered strong if the ratio was greater than 1.0, moderate when the scale was between 0.5 and 1, and weak if it was less than 0.5 (Gao et al. 2020).

Species identification

The spore suspensions of B12 were inoculated and grown on MEA with 3% sea salt, 28 °C for 5 days. The colony was observed and characterized, including size, texture, color, soluble pigments, and exudates. Microscopic examination was then performed on spores and hyphae followed by lactophenol cotton blue (LPCB) staining (Leck 1999) through a BA210 light microscope (Motic, China).

Internal transcribed spacer (ITS) has been widely approved as a DNA barcode for the taxonomic identification of fungi (Lee et al. 1992; Hinrikson et al. 2005). As described, ITS sequence was amplified from the strain genome to perform a phylogenetic analysis (Gao et al. 2020). Phylogenetic trees were constructed by the dataset of homologous ITS sequences from various species, using maximum-likelihood (ML) analysis in MEGA7.

Genome sequencing

The significantly antibactericidal activities of B12 highlighted the necessity for further study on the strain, especially on the secondary metabolites (SMs) and associated genes, for which, whole-genome analysis certainly was a reliable approach. Hence, the genome of B12 were sequenced on the Illumina MiSeq sequencing platform (Genewiz Co, China).

In brief, the construction of DNA libraries was performed using 100 ng genomic DNA, which was randomly fragmented to 500 bp by sonication (Covaris S220, USA). Sequencing was subsequently performed using a 2 × 150-bp paired-end (PE) configuration; image analysis and base calling were performed using HiSeq Control Software. The adapter and low-quality sequences were removed from the raw sequencing data by cutadapt (v1.9.1). The ideal reads were assembled and gap-filled using Velvet (Zerbino and Birney 2008), SSPACE (Boetzer et al. 2011) and GapFiller (Boetzer and Pirovano 2012), respectively. All genome sequencing data have been submitted to the NCBI SRA database (accession NO.: PRJNA714189). The genomic sequence of B12 was analyzed on the antiSMASH (Blin et al. 2019) server with the ClusterFinder algorithm to predict the potential biosynthetic gene clusters (BGCs) and the corresponding SMs.

Gene prediction and functional annotation

The software Augustus (version 3.3) (Stanke et al. 2006) was used to predict coding genes and high-GC regions. Based on the homology-dependent approach, the assembled sequences were mapped to the reference genome A.
terreus NIH2624. Following the alignment against the NCBI nr database by BLAST, the coding genes were functionally annotated in Kyoto Encyclopedia of Genes and Genomes (KEGG) and Carbohydrate Active enZymes (CAZymes) database (Consortium 2004) (Kanehisa et al. 2019). In addition, the predicted proteins were classified by the Cluster of Orthologous Groups of proteins (COG) database (Tatusov et al. 2003).

Results

Antibacterial activities screening

A range of pathogenic bacteria were used to evaluate the antimicrobial property of B12. As shown in Fig. 1, the fermented products of strain B12 displayed a broad-spectrum antibacterial activity against all select tested microorganisms. Compared with the Gram-negative pathogens (*E. coli*, *A. baumannii*, *K. aerogenes*, *P. aeruginosa*) tested in the study, B12 demonstrated more potent antimicrobial effects against Gram-positive bacteria (MRSA, MRSE, *M. luteus*, *S. aureus*), parallel to that of standard antibiotics (chloramphenicol, 0.1 mM). In view of the unique ecological fitness, further genetic and physiological investigations are necessary on the strain to unveil the underlying bioactive components and possible synthetic profiles.

Morphological and phylogenetic analysis

In microbial taxonomy, classic species features, such as morphological, physiological, and genetic characteristics have become essential and canonical approaches. Fungal morphology and ITS sequences were used for taxonomic identification for the strain B12 in this study.

The morphology of colonies was observed after incubation at 28 °C for 5 days (Fig. 2A). The colonies raised white, circular and flocculose, slightly convex, with lanose, and filiform margin. At the reverse side, colonies were brownish orange at the center, desaturating to gray-pale margin, without soluble pigment or exudate diffusing to the agar. Microscopy showed that mycelium grows filiform, while small and globose conidia stack to form compact conidial heads. Macroscopically or microscopically, the strain B12 could be identified as *Aspergillus* sp., which certainly required further identification by molecular techniques.

Owing to the highest resolving power for discriminating closely related species, ITS sequences have been adopted as a standard DNA barcode for fungi (Schoch et al. 2012). In our study, based on the ITS sequences, a phylogenetic tree was constructed, which clearly delineated species delimitation between *Cladosporium* and *Aspergillus*. Consistent with morphological characterization, B12 was clustered into *Aspergillus* clades, supported by the highest identity scores and 100% bootstrap value. More specifically, the strain closely associated with *A. terreus*, forming a sister taxon with *A. niger* clade (Fig. 2B).

![Antibacterial activities](image-url)
Fig. 2  Morphologic and phylogenetic analysis on strain B12.  
A Morphology of B12. Colony and microscopic morphology after 5 days cultivation at 28 °C on MEA. Upper: obverse and reverse side of colonies; down: conidiophores and conidigenous at 40 × magnification (scale bar 10 μm). B Maximum-likelihood tree of B12. Multiple sequence alignment was conducted using Clustal W (default settings), and phylogenetic relationships were based on ML analysis with 1000 bootstrap replications in MEGA7
**Genome information of B12**

As genome-wide analysis provides first insights into the nature of microbial functioning (Zhu et al. 2016), the genome of B12 was sequenced with a coverage of 173.87×. The draft genome was assembled into a total size of 29.51 Mb, with a G+C content of 52.31%, composing 80 scaffolds. The average length of consensus contigs was 368,922.8 bp with an N50 of 1603,970 bp. The protein-coding regions were predicted through Augustus software, resulting in a total of 10,148 protein-coding genes with an average length of 1548.28 bp (Table 1).

**Functional annotation**

As far as the structural–functional correlation is concerned, the function of genes and the presumptive encoding products can be homology-dependently predicted (Alberts et al. 2002). Practically, functional annotations for the protein-coding genes in the genome yielded a generally consistent profile against CAZy, KEGG, and COG database: a large number of genes involve in metabolic pathways, indicating a vigorous potency in biochemical metabolism. According to the KEGG analyses, 4,204 coding genes were annotated, assigned to 332 pathways, which could be classified into 6 functional categories: cellular processes, Environmental Information Processing, Genetic Information Processing, Human Diseases, Metabolism, Organismal Systems (Fig. 3). Among the metabolic processes, the subcategory of SMs biosynthesis was conspicuous for the significant abundance and diversity (11.94%), besides the primary metabolism (e.g., amino acid, carbohydrates, and lipid metabolism), underlining the potential biosynthetic capabilities of the strain.

Based on carbohydrate-active enzyme (CAZy) annotation, 1984 proteins were predicted to be CAZymes, accounting for 19.55% of the total proteins encoded by B12 genome. The putative CAZymes comprised 6 groups: Carbohydrate-Binding Modules (CBMs), Auxiliary Activities (AAs), Carbohydrate Esterases (CEs), Polysaccharide Lyases (PLs), Glycosyl Transferases (GTs), Glycoside Hydrolases (GHs). Among those subfamilies, CBMs (27.92%), GTs (26.66%), and GHs (33.77%) combined to constitute the majority of CAZymes (~ 88.36%; Fig. 4). Presumably, the multifarious CAZymes could be a survival strategy for nutrient acquisition and niche adaptation, in terms of their potency and versatility in carbohydrates degradation and biotransformation (Chettri et al. 2020).

In COG database, 6,886 protein-coding genes were assigned to 24 categories, which represented 67.86% of the total coding sequences. The preponderance of metabolism class (II) was coincidently demonstrated by the considerable proportion (57.39%) in COG functional categories (Fig. 5), successively followed by poorly characterized function (IV; 26.20%), information storage processing (III; 15.93%), and intracellular processes (I; 13.64%). Specifically, in the metabolism (II), the bioprocesses associated with SMs category appeared rather prominent, represented by the relative proportion to total (4.53%), which might confer a biochemical flexibility and adaptive superiority to the strain.

**Prediction on the biosynthesis capabilities**

Different functional annotation systems have integrated to highlight the biosynthetic potential in strain B12, possibly contributing to its antimicrobial activities. As for fungal genomes, the genes that associated with SMs were often clustered, referred to as BGCs (Bok et al. 2006). Hence, the speculative BGCs in B12 were predicted by antiSMASH database, forwarding 67 BGCs. In terms of biosynthetic paradigms, those BGCs were comprised of 10 types (Fig. 6): NRPS (27), PKS (17), NRPS–indole hybrid (5), NRPS–T1PKS hybrid (5), NRPS–betalactone (1), NRPS–terpene hybrid (1), terpene (5), indole (4), betalactone (1), siderophore (1).

The fertile and multifarious BGCs, supposedly underlie the biosynthetic dexterity to produce novel chemical backbones or natural products, which certainly merits more exploration. Sequence alignment underscored 8 BGCs with 100% similarity to known BGCs, corresponding to a range of structurally diversified natural products: clavaric acid, dihydroisoflavipucine/isoflavipucine, dimethylcoprogen, alternariol, aspterric acid, and pyranonigrin E (Fig. 7). In terms of the structural–functional correlations, the chemical diversity of inferred SMs supposed to entail various roles, which have been demonstrated by cumulative reports, comprising antitumor [clavaric acid (Godio et al. 2007)] and antioxidative [pyranonigrin E (Shindo et al. 2014)] agents, siderophores [dimethylcoprogen (Jalal et al. 2007)], plant growth regulator (aspterric acid (Zaehele et al. 2014)), and phytotoxins [alternariol (Solhaug et al. 2016), dihydroisoflavipucine/isoflavipucine (Brock and Biology 2011)]. Besides variance in the proposed

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**Table 1** General features of the B12 genomes

| General features          | Value     |
|---------------------------|-----------|
| Assembly size (Mb)        | 29.51     |
| G+C (%)                   | 52.31     |
| Assembled scaffolds       | 80        |
| N50 length (bp)           | 1,603,970 |
| Average length (bp)       | 368,922.8 |
| Predicted protein-coding genes | 10,148   |
| Average length predicted protein-coding genes | 1,548.28 |
| Average depth of reads cover | 173.87  |
Fig. 3  KEGG classifications of protein-coding genes in the B12 genome. Red bar: Cellular Processes; Brown bar: Environment Information Processing; Green bar: Genetic Information Processing; Cyan bar: Human Diseases; Blue bar: Metabolism; Purple bar: Organismal Systems

Fig. 4  Putative CAZymes coded by the genome of B12
products, the diversification of biosynthetic patterns was equally inspirational, involving T1PKS (Fig. 7A–C), NRPS–PKS hybrid (Fig. 7D–E), NRPS (Fig. 7F), terpene (Fig. 7G–H), which might imply a pluripotent biochemical toolkit in this strain, as determined from the current limited genome-mining scope.

In addition, a gene cluster homologous (~44%) to the BGC of monacolin K (MK/lovastatin) was found in B12
As the inhibitor of HMG CoA reductase (Alberts et al. 1980), Lovastatin was originally obtained from a soil-derived *Aspergillus terreus* strain (Mulder et al. 2015), and also produced by other fungal genera like *Penicillium*, *Paecilomyces*, *Trichoderma*, and *Pleurotus ostreatus* (Miranda et al. 2014). Despite the considerable similarity of genes organization and sequence identity (> 70%), the region in B12 exhibited an obvious different pattern from MK/lovastatin biosynthetic pathway, reflected by the absence of *lovE*, and distinct truncation of *lovF*. Insofar as is known, *lovE* gene encodes a transcription factor that regulates MK/lovastatin gene cluster, whereas *lovF* encodes a diketide synthase (DKS), one of the two polyketide synthases involved in MK/lovastatin biosynthesis (Barrios-González et al. 2020), underlying the indispensability of either part. We failed to obtain lovastatin from the fermented products of B12,
appearing plausible from the perspective of biosynthetic mechanism.

**Chemical isolation and characterization of metabolites**

To interpret the biosynthetic capacities of B12, the fermented products of strain B12 were extracted for SMs isolation and purification. Subsequently, a range of metabolites was identified by chemical separation and characterization, which differed in panel structure and relative abundance, including terrein (1), butyrolactone I (2), terretonin E (3), terretonin A (4), acoapetaline B (5), epi-aszonalenins A (6) (Fig. 9).

Via chromatographic separation and HNMR determination, the compound terrein (1) was purified as yellow crystal needles, which is addressed as a *A. terreus* metabolite with ecological, antimicrobial, antiproliferative, and antioxidative activities (Zaehle et al. 2014). Based on the chemical clue, a BGC presumably for terrein synthesis was found in region 9.4 (Fig. 10B), demonstrating a high degree of amino acid sequence homology (> 72%) with the counterpart of *A. terreus* NIH2624 (Yin et al. 2016). However, despite the approximate gene composition and sequence identity, the assumed BGC was deprived of terH-J genes. In the case of terrein production, a gene locus comprised by terA–J and transcriptional regulator terR, was characterized to encode the biosynthetic process (Zaehle et al. 2014). As terG and terI were depicted as MFS transporters, while function of terH–I was ambiguous, deletion of them putatively would lead to a diminution instead of abolition of terrein generation (Yin et al. 2016), which seemed to be substantiated in our study.

Besides terrein, butyrolactones and terretonins are also frequently reported as typical SMs produced by *A. terreus* (Guo and Wang 2014). Hence, from the point of SMs production, the presence of those metabolites apparently complied with the species-specific descriptions on biosynthetic
profiling. In contrast, as for acoapetaline B (5) and epi-aszonalenins A (6), there was little information available, with limited clues in the original organisms and structural characterizations. It was reported that acoapetalines were isolated from plants (Hu et al. 2018; Xie et al. 2019), while epi-aszonalenins derived from *A. novofumigatus* (Rank et al. 2006), ostensibly divergent from *A. terreus*. The identification of those compounds in strain B12 might be ascribed to the plentiful (33.85%) uncharacterized BGCs to some extent, in terms of the pendent and elusive insight of the biosynthetic processes and corresponding products in *A. terreus* (Guo and Wang 2014), which awaits more advance of genome mining and genetic approaches.

**Discussion**

*Aspergillus terreus*, widely distributed in terrene and marine environment, has become a prolific producer of numerous bioactive agents, such as lovastatin, sulochrin, terrein, itaconic acid, etc. (Rateb and Ebel 2011). In the recent years, this fungus derived from ocean became more attractive, as concerning the structurally unique or biologically active metabolites (Zhang et al. 2017). In this study, an *A. terreus* strain B12 was isolated from sponges in the South China, which promisingly demonstrated broad bacteriostatic effects against a range of pathogenic bacteria. The whole genome was sequenced followed by comparative genomics analysis and functional annotations, leading to a total of 67 putative BGCs. However, only a fraction of putative BGCs (18) possessed a high sequence similarity (≥ 50%) with annotated BGCs in the MIBiG database, in contrast with a variety of uncharacterized gene clusters, conjecturally which might provide a biosynthetic blueprint for the products diversification in the strain. The speculation was partially confirmed by chemical separation, which identified several compounds, consisting of SMs commonly in *A. terreus* (terrein, butyrolactone I, and terretomin) or not (acoapetaline and epi-aszonalenins).

Besides the excellent ecological adaptability, *A. terreus* is an illustrious strain in the industrial production of lovastatin, a valuable cholesterol-lowering agent for hyperlipidemia treatment (Tobert 2003). Lovastatin inhibits hydroxyl methyl glutaryl coenzyme A reductase (HMG CoA), the key enzyme of cholesterol biosynthesis, which is supposed as an adaptive strategy to halter fungal ergosterol generation, required for the maintenance of cytoplasmic membrane integrity (Keller 2015; Rodrigues 2018). The lovastatin biosynthesis is encoded by a BGC (*lov*) containing 18 genes, among which, five genes (*lov*A, B, C, D, and F) have been identified to encode essential enzymes, while *lov*E acts as transcription factor, positively controlling the biogenic route (Kennedy et al. 1999; Campbell and Vederas 2010). However, as for the homogenous BGC within B12 genome, the
deletion of \textit{lovE} and a significant truncation of \textit{lovF} were detected, which assumingly would abolish lovastatin production. In terms of the synthetic logic of lovastatin, which actually provides a biochemical aid for fungal self-protection (Zhgun et al. 2019), the acquisition of \textit{lov} BGC by horizontal gene transfer might actually depend on the niche competitive status. The biosynthetic impuissance due to gene deficits had been reported in an endophytic \textit{A. terreus} strain (Savitha et al. 2014), which possibly should ascribe to the primitive symbiotic environments of the strain above-mentioned or B12, for the comparable, but diverse philosophy. The substantial biosynthetic potential was highlighted by genome mining within B12, depicted by various uncharacterized BGCs, which requested the corresponding linkage with the product. However, compared with lovastatin, many other synthetic processes still remains elusive, even within the best understood genome of \textit{A. terreus} (strain NIH 2624) (Guo and Wang 2014). For instance, terretonins and butyrolactone \textit{i} had been isolated from fermented extract of B12, which were adopted as major metabolites of \textit{A. terreus} and physiological regulators in response to ecological competition (Schimmel et al. 1998; Louis et al. 2017). It had been proposed that a compact cluster (\textit{trt}) was responsible for terretonin biosynthesis, although conversion process to the end product (terretonin) remained ambiguous, which might involve other genes in different loci (Guo et al. 2012); Although a NRPS-like gene \textit{btyA} was presumed to encode the core enzyme for the backbone of \textit{γ}-butyrolactone in \textit{A. terreus} (Guo et al. 2013). Whereas, according to the sequence homology, the attempt to assign those products to potential BGCs within the B12 genome led to a failure, probably due to currently obscure understanding on secondary metabolic pathways, especially given the possibility of isozymes or orthologs presented in the unknown BGCs, which could lead to partly overlapping biosynthetic routes.
and presumably more complicated scenarios (Chun-Jun et al. 2015; Hossain et al. 2016).

Among the SMs isolated from the strain B12, terrein (1) and butyrolactone I (2) were the predominant products, with relatively abundant yields, which corresponded to the descriptions as representative metabolites of A. terreus in previous observations. As reported, terrein and butyrolactone I exhibited antibacterial activities against Gram positive bacteria to some extents (present in another paper), which at least partially explained the bacteriostatic effects of fermentation products of the strain. However, due to the extremely low outputs, current study failed to provide bioactive information on other compounds, terretonin A & E, acoapetaline B, epi-aszonalenins A, which probably were ascribed to the low level of biosynthesis, and the difficulties in chemical separation as well. In view of the relatively limited knowledge on these SMs, further investigations were necessary, through enlarged cultivation, and products accumulation, which would shed some light on their structure–function relationships.

**Conclusion**

In our study, the combination of genome mining and chemical separation, although far from comprehensively, have underscored the metabolic potencies of the A. terreus strain B12, which might ascribe to the exclusively biological plasticity for niche acclimatization. The specific metabolites and BGCs, either characterized or not, presumptively could contribute to the defensive mechanisms and survival strategies for the strain, in light of the harshness and rivalrousness of marine environment. Our work shed more light on the genetic and biological profiling of marine-derived A. terreus, which might facilitate further investigation and development of the valuable microorganisms.

**Acknowledgements** This work was supported by funds from the National Key R&D Program of China (2018YFC0311000), the Priority Academic Program Development of the Jiangsu Higher Education Institutions (PAPD).

**Declarations**

**Conflict of interest** The authors declare no conflict of interest.

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