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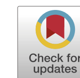
Research Article

Biotransformation of natural polyacetylene in red ginseng by *Chaetomium globosum*



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ABSTRACT

Background: Fermentation has been shown to improve the biological properties of plants and herbs. Specifically, fermentation causes decomposition and/or biotransformation of active metabolites into high-value products. Polyacetylenes are a class of polyketides with a pleiotropic profile of bioactivity.
Methods: Column chromatography was used to isolate compounds, and extensive NMR experiments were used to determine their structures. The transformation of polyacetylene in red ginseng (RG) and the production of cazaldehyde B induced by the extract of RG were identified by TLC and HPLC analyses.
Results: A new metabolite was isolated from RG fermented by *Chaetomium globosum*, and this new metabolite can be obtained by the biotransformation of polyacetylene in RG. Panaxytriol was found to exhibit the highest antifungal activity against *C. globosum* compared with other major ingredients in RG. The fungus *C. globosum* cultured in RG extract can metabolize panaxytriol to Metabolite A to survive, with no antifungal activity against itself. Metabolites A and B showed obvious inhibition against NO production, with ratios of 42.75 ± 1.60 and 63.95 ± 1.45% at 50 μM, respectively. A higher inhibitory rate on NO production was observed for Metabolite B than for a positive drug.
Conclusion: Metabolite A is a rare example of natural polyacetylene biotransformation by microbial fermentation. This biotransformation only occurred in fermented RG. The extract of RG also stimulated the production of a new natural product, cazaldehyde B, from *C. globosum*. The lactone in Metabolite A can decrease the cytotoxicity, which was deemed to be the intrinsic activity of polyacetylene in ginseng.
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1. Introduction

Red ginseng (RG), a widely used traditional herbal medicine, is reported to have enhanced pharmacological activities and stability compared with fresh ginseng because of changes in its chemical constituents [1], and it is one of the most popular herbal medicines to be used as a dietary supplement in recent years. Ginseng contains various pharmacologically active compounds such as ginsenosides, polysaccharides, polyacetylenes, and phytosterols. Among these compounds, ginsenosides are considered major bioactive compounds [2]. The fermentation process has been shown to improve the biological properties of plants and herbs. More specifically, fermentation causes decomposition and/or biotransformation of active metabolites into high-value products [3]. Previous work has reported that ginseng modified by fungal and bacterial fermentation has improved bioavailability and increased the amount of bioactive components [4]. However, only a few studies focused on the metabolites from fermented red ginseng (FRG), and most of this research focused on the metabolic mechanism of ginsenosides [5]. Therefore, in the present work, we investigated the compounds from RG fermented by *Chaetomium globosum*. *Chaetomium* is considered to be a rich source of active compounds. These metabolites produced by *Chaetomium* belong to diverse chemical groups, including chaetoglobosins, xanthones, anthraquinones, chromones, depsidones, terpenoids, and steroids, and many of these compounds showed enzyme inhibitory,

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cytotoxic, antitumor, antimalarial, antibiotic, and other activities [6]. A new metabolite (Metabolite A) associated with RG was isolated from FRG, and this is the first report on the biotransformation of natural polyacetylene. Polyacetylenes are a class of polyketides that occur in plants, fungi, marine organisms, and animals. These compounds show a pleiotropic profile of bioactivity [7,8]. A series of biologically active polyacetylenes were isolated from the *Panax ginseng* root. Among them, panaxytriol (PXT) was reported to have *in vitro* cytotoxic activity against a range of human tumor cells [9]. The PXT-based compounds are markedly able to alleviate the toxic and neuropathy-inducing side effects associated with chemotherapeutic and radiation-based anticancer treatments [10]. A new natural product, cazaldehyde B (Metabolite B) (Fig. 1), was also found in this work, and it was proved to be produced by *C. globosum* through the induction of RG extract.

2. Materials and methods

2.1. General experimental procedure

Silica gel (200−300 mesh; Qingdao Marine Chemical Group Co., Shangdong, China), the TLC plate (Qingdao Marine Chemical Group Co.,Shangdong, China), Lichroprep RP-18 (Beijing Greenherbs Science and Technology Development Co., Beijing, China), and Sephadex LH-20 (GE Healthcare Co.,Buckinghamshire, UK) were used for column chromatography and chromatography analysis.1D and 2D NMR spectra were obtained on Bruker AVANCE 500 MHz NMR instruments (Bruker, Karlsruhe, Germany). MS spectra were recorded with Agilent G3250AA (Agilent, Santa Clara, CA, USA) and AutoSpec Premier P776 spectrometers (Waters, Milford, USA). Optical rotations were obtained on a Jasco P-1020 polarimeter(Tokyo, Japan). HPLC analyses were performed on a Waters e2695 instrument(Milford, USA) with Agilent ZORBAX SB-C18(Santa Clara, USA). Circular dichroism spectra were obtained on an Applied Photophysics Chirascan spectrometer (Applied Photophysics Ltd., Surrey, United Kingdom).

2.2. Chemicals

PXT and two ginsenosides, ginsenoside Rg3 and ginsenoside Rh1, were isolated from RG, and their structures were determined by NMR.

2.3. Biological material and cultivation of the fungal strain

RG was obtained from the Jianzhijia Pharmacy of Kunming in Yunnan Province in China. The fungus was isolated from *Dendrobium officinale* in Honghe in Yunnan Province. The species was identified as *C. globosum* (GenBank accession no. KX926579) on the basis of morphological and genetic internally transcribed spacer (ITS) characteristics. A voucher specimen was deposited at the School of Chemical Science and Technology, Yunnan University. The fermentation of *C. globosum* was carried out in 0.5-L Erlenmeyer flasks containing 120 mL of potato dextrose broth (PDB; potato infusion of 200 g of fresh potato, 15 g of dextrose, and 1.0 L of distilled water; pH 7.0) at 150 rpm and 28°C for 2 days for a seed culture. Aliquots of 20−25 mL of seed culture were transferred to a 1.0-L Erlenmeyer flask containing 200 mL of RG extract (5.5 kg of RG, 30 L of distilled water; pH 7.0) and incubated at 150 rpm and 28°C for 7 days. The routine fermentation of *C. globosum* was carried out in 0.5-L Erlenmeyer flasks containing 120 mL of PDB (potato infusion of 200 g of fresh potato, 15 g of dextrose, and 1.0 L of distilled water; pH 7.0) with the same method as that used for FRG. The precursor PXT was added in the routine fermentation at a concentration of 2 mg/200 mL.

2.4. Extraction and isolation

The culture medium was filtered to remove mycelia. The filtrate was partitioned with ethyl acetate (EtOAc) to produce an EtOAc layer and then dried under vacuum to afford a dark brown residue (21.6 g). The extract was subjected to column chromatography on silica gel and was eluted with a gradient of CH_2Cl_2−MeOH from 1:0 to 0:1 (v/v) to obtain five fractions (A−E). Fraction B (1.8g) was separated using Sephadex LH-20 (CH_2Cl_2−MeOH at 1:1) to obtain seven subfractions (B1−B7). Fraction B1 was purified by Lichroprep RP-18 column chromatography with MeOH−H_2O (80%) to produce Metabolite B (10 mg). Fraction B2 was separated repeatedly using Sephadex LH-20 (CH_2Cl_2−MeOH at 1:1) to obtain five subfractions (B21−B25). Fraction B23 was separated by Lichroprep RP-18 column chromatography with MeOH−H_2O 20% to obtain Metabolite A (7 mg).

Metabolite A. [α]22 D -78.5 (c 0.2, MeOH). High Resolution Electrospray Ionization Mass Spectrometry (HRESI-MS) *m/z*: 257.0785 $[M+Na]^+$, calcd for $C_{13}H_{14}O_4Na^+$: 257.0790. ^{1}H-NMR ($CDCl_3$, 500 MHz) and ^{13}C-NMR ($CDCl_3$, 125 MHz) in Table 1.

Metabolite B. HRESI-MS *m/z*: 301.1409 $[M+Na]^+$, calcd for $C_{16}H_{22}O_4Na^+$: 301.1416. ^{1}H-NMR ($CDCl_3$, 500 MHz) and ^{13}C-NMR ($CDCl_3$, 125 MHz) in Table 2.

2.5. TLC and HPLC analysis method

The extracts of RG, FRG, and routine fermentation products using the PDB medium were obtained according to the aforementioned method. Similar sampling volumes of RG, FRG, routine fermentation products, PXT, and Metabolites A and B were prepared for use in the TLC test. TLC was used for qualitative identification of PXT and Metabolites A and B in extracts of RG, FRG, and routine fermentation products, using $CHCl_3$−MeOH (10:1) as a developing solvent. The visualization reagents were iodine vapor and sulfuric acid−anisaldehyde.

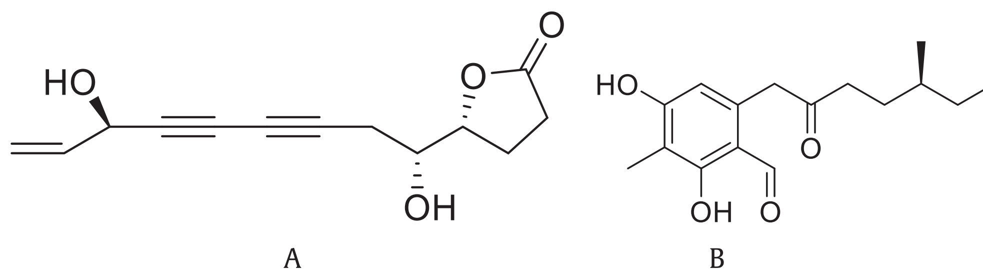

Fig. 1. Structures of botanical Metabolite A associated with red ginseng from fermented red ginseng by biotransformation of endophytic *Chaetomium globosum*, and fungal Metabolite B produced by *C. globosum* induced by RG extract.
RG, red ginseng.

Table 1
^{13}C-NMR and ^{1}H-NMR data of Metabolite A

Position	A	
	δ_H (*J* in Hz)	δ_C
1	5.46 (d,17.0), 5.26 (d,10.0)	117.3
2	5.96 (m)	135.9
3	4.92 (d, 5.0)	63.5
4		75.2
5		70.7
6		67.0,
7		77.0
8	2.68 (m), 2.65 (m)	24.7
9	3.82 (m)	71.6
10	4.63 (m)	80.8
11	2.34 (m), 2.22 (m)	24.0
12	2.62 (m), 2.54 (m)	28.5
13		176.9

Table 2
^{13}C-NMR and ^{1}H-NMR data of Metabolite B

Position	B	
	δ_H (*J* in Hz)	δ_C
1	9.84 (s)	192.6
2		136.9
3		164.4
4		110.8
5		161.4
6	6.16	110.8
7		112.9
8	3.92 (s)	45.8
9		208.5
10	2.54 (m)	40.4
11	1.30 (m), 1.62 (m)	30.3
12	1.32 (m)	34.0
13	1.14 (m), 1.40 (m)	29.2
14	0.86 (t, 7.0)	11.3
15	2.06 (s)	7.00
16	0.84 (d, 6.0)	18.9
3-OH	12.6 (s)	

The HPLC method was as follows: the RG blank (118.6 mg), FRG (9.9 mg), the PDB medium (4.5 mg), the PDB medium supplemented with PXT as a precursor (7 mg), PXT (1.8 mg), and Metabolite A (1.3 mg) were dissolved in 3.5 mL, 1.5 mL, 1.5 mL, 1.5 mL, 1.5 mL, and 1.0 mL of MeOH, respectively, with a sample size of 10 μL. A gradient solvent (acetonitrile/H_2O: 10% to 100%; t_R: 0 to 30 min, acetonitrile/H_2O: 100% to 100%; t_R: 30 to 35 min) and a flow rate of 0.8 mL/min were used for HPLC with a detection wavelength of 250 nm.

2.6. Bioactive assay

In the *in vitro* antimicrobial test, PDB was used as an incubation medium for fungus. The final volume of each well was 100 μL. Aliquots (5 μL) of the metabolite solutions in dimethyl sulfoxide were added to sterilized 96-well microplates, and their final concentrations ranged from 512 to 1 μg/mL, using a twofold serial dilution method. Spore suspensions were inoculated in each well. Wells containing pathogenic fungus suspensions, dimethyl sulfoxide, and the incubation medium were used as negative controls, and the wells containing nystatin were used as the positive control with a minimum inhibitory concentration (MIC) of 32 μg/mL.

The nitric oxide (NO) inhibitory activity of these compounds was determined using the Griess reagent assay for NO production. In brief, the murine macrophage cell line was used as a detection model. The supernatants were used to measure NO production with a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay for cell viability. L-monomethylarginine (L-NMMA) was used as the positive control with a ratio of 54.07 ± 1.65% at a concentration of 50 μM.

The cytotoxicity of Metabolites A and B against tumor cells, HL-60, A-549, SMMC-7721, SW480, and MCF-7, was assessed *in vitro* by means of a 3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethoxyphenyl)-2-(4-sulfopheny)-2H-tetrazolium assay. The positive control of Taxol was used with $IC_{50} < 0.008$ μM.

3. Results and discussion

3.1. Structural elucidation

Metabolite A was obtained as a yellow oil and was determined to be $C_{13}H_{14}O_4$ from its distortionless enhancement by polarization transfer (DEPT) spectrum and HRESI-MS (*m/z* 257.0785 for $[M+Na]^+$). Analysis of its ^{13}C-NMR data indicated the presence of one CO at δ: 176.9; one olefinic methine at δ: 135.9; one olefinic methylene at δ: 117.3; three methines at δ: 80.8, 71.6, and 63.5; two alkynyls at δ: 77.0, 75.2, 70.7, and 67.0; and three methylenes at δ: 28.5, 24.7, and 24.0. Based on the 7 degrees of unsaturation of $C_{13}H_{14}O_4$, an additional ring existed in this compound. The analysis of correlation spectroscopy data revealed the C_1—C_2—C_3 fragment and the C_8—C_9—C_{10}—C_{11}—C_{12} structural connection. The heteronuclear multiple bond correlations from H-3 to C-1, C-2, C-4, and C-5; H-8 to C-6, C-7, and C-10; H-9 to C-7; H-11 to C-10; H-11 to C-12 and C-13; and H-12 to C-13 confirmed the structure of Metabolite A (Fig. 2). The connection of C-10 and C-13 was confirmed by a downfield shift of H-10 and C-10 at 4.63 (m) and 80.8. Because of the high degree of similarity between the structures of Metabolite A and PXT [9], a cytotoxic polyacetylene frequently found in ginseng, Metabolite A, should be biotransformed from polyacetylene in RG by microbial fermentation (Fig. 3). We also confirmed the polyacetylene biotransformation determined by the TLC analysis (Fig. S11). This biotransformation involves the lactonization of PXT (Fig. 3), where the microbial lactonization had stereoselectivity according to the bioprecursor [11]. The configurations at C-9 and C-10 were determined to be *R* by comparing NMR and an optical rotation (OR) value with those of muricatacin [12], and this elucidation also was in accordance with the stereochemistry of PXT. The configuration of PXT at C-3 was essential in the OR values, with OR values $[\alpha]_D = -12.3$ for (3*R*, 9*R*, 10*R*)-PXT and $[\alpha]_D = 25.3$ for (3*S*, 9*R*, 10*R*)-PXT [13]. The configuration of Metabolite A at C-3 was determined by comparing the NMR and OR values with those of PXT, with the biogenesis of Metabolite A being biotransformed from PXT. The OR value at -78.5 and circular dichroism spectrum of Metabolite A also confirmed the absolute configuration by comparing with those of natural PXT ($[\alpha]_D$ -18.4) (Fig. S18, S19) [9]. The chemical transformation failed to determine the configuration for the low amount of Metabolite A.

Metabolite B was determined to be cazaldehyde B, which has been previous produced by synthetic biology methods [14]. The

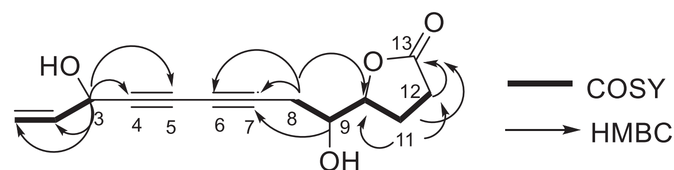

Fig. 2. ^{1}H—^{1}H correlation spectroscopy (COSY) correlations and the selected heteronuclear multiple bond correlation (HMBC) correlations of new metabolite (Metabolite A) produced from fermented red ginseng by the microorganism biotransformation of polyacetylene.

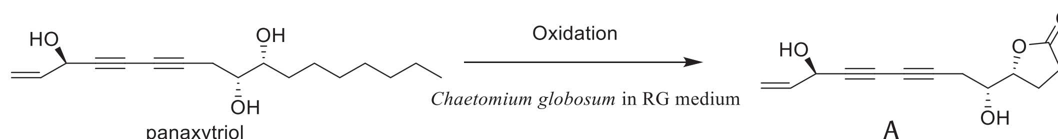

Fig. 3. The plausible biotransformation of Metabolite A produced from fermented red ginseng by microorganism biotransformation of *C. globosum*.
RG, red ginseng.

structure of Metabolite B was determined by comparing NMR data with those of cazaldehyde B and MS analysis. Analysis of its ^{13}C-NMR data indicated the presence of three methyls at δ: 7.0, 11.3, and 18.9; two methines at δ: 110.8 and 34.0; four methylenes at δ: 45.8, 40.4, 30.3, and 29.2; six quaternary carbons at δ: 208.5, 164.4, 161.4, 136.9, 112.9, and 110.8; and an aldehyde group at δ: 192.6, which showed the skeleton of cazaldehyde B [14]. The configuration of Metabolite B was determined by comparing the NMR with that of chaetomugilins A–F, and the stereochemistry of C-12 was consistent with the related analogs [15]. This is the first time cazaldehyde B has been isolated from natural sources. Based on the TLC test (Fig. S13), Metabolite B was only found in FRG extract and not in *C. globosum* extract cultivated in the PDB medium.

3.2. The detoxication mechanism of C. globosum against the inhibition of active compounds from RG and evaluation of inhibition of NO and cytotoxicity of Metabolites A and B

In FRG, because the active metabolites in RG may affect the growth of *C. globosum*, *C. globosum* may possess a detoxication mechanism against such inhibition. To study the interaction of the active ingredients from RG and *C. globosum* in the FRG system, the antifungal activities of the new metabolite (Metabolite A), the main ginseng ingredients (PXT, ginsenoside Rg3, and ginsenoside Rh1) thought to inhibit *C. globosum* growth were investigated. PXT showed the highest antifungal activity with an MIC of 128 μg/mL, compared with those of Metabolite A (MIC > 512 μg/mL) and two ginsenosides (MIC > 512 μg/mL). These results suggest that *C. globosum* can biotransfer PXT to Metabolite A with less toxicity than PXT for its own survival. Metabolites A and B showed obvious inhibitions against NO production with ratios of 42.75 ± 1.60 and 63.95 ± 1.45% (IC_{50} at 40.12 ± 0.85 μM) at concentrations of 50 μM, respectively. A higher inhibitory rate on NO production was observed in Metabolite B than in a positive drug. However, Metabolites A and B exhibited no obvious cytotoxicity at 40 μM.

3.3. The analysis of Metabolites A and B and PXT in different culture conditions by TLC and HPLC tests

Based on the TLC test, the new metabolite (Metabolite A) was found to be negative in RG extract but positive in FRG. PXT was positive in both RG and FRG extracts (Fig. S11, S12, S14 and S15). Polyacetylenes, including PXT in FRG, were not isolated; thus, Metabolite A was obtained by microbial fermentation. Metabolite B was positive in FRG extract but negative in *C. globosum* cultured in the PDB medium (Fig. S13). Thus, the RG extract induced the production of cazaldehyde B (Metabolite B). The content of PXT in the RG extract was 0.872 mg/mL by HPLC analysis (Fig. S16).

3.4. The biotransformation of polyacetylene in FRG

PXT is a major product from ginseng that exhibits significant cytotoxicity. The new metabolite (Metabolite A) was isolated from FRG, and the structures of Metabolite A and PXT exhibited high similarity. We also confirmed through TLC and HPLC analyses that Metabolite A does not exist in the RG extract (Fig. S11, Fig. S14). To study the biotransformation of polyacetylene by *C. globosum*, we added the precursor PXT to *C. globosum* cultured in the PDB medium. However, HPLC analysis showed that Metabolite A and PXT did not exist in the extract of the PDB medium using PXT as a precursor (Fig. S14, S15). Furthermore, Metabolite A could not be isolated by column chromatography in this medium (1 L sample). This suggests that the biotransformation from PXT to Metabolite A by *C. globosum* occurs in the RG medium. The genus *Chaetomium* has been shown to transfer other natural products to its oxydate in previous works [16,17].

4. Conclusion

The new metabolite (Metabolite A) is a rare example of a natural polyacetylene biotransformed by microbial fermentation. This biotransformation only occurs in FRG. The RG extract also stimulated the production of a new natural product, cazaldehyde B, from *C. globosum*. The fungus *C. globosum* cultured in RG extract can metabolize PXT to Metabolite A to survive with no antifungal activity against itself. The lactone in Metabolite A can decrease the cytotoxicity, which was deemed to be the intrinsic activity of polyacetylene in ginseng. Metabolites A and B showed obvious inhibition against NO production with ratios of 42.75 ± 1.60 and 63.95 ± 1.45% at 50 μM, respectively.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2019.06.007.

References

[1] Im K, Kim J, Min H. Ginseng, the natural effectual antiviral: protective effects of Korean Red Ginseng against viral infection. J Ginseng Res 2016;40:309–14.
[2] Lee SM, Bae BS, Park HW, Ahn NG, Cho BG, Cho YL, Kwak YS. Characterization of Korean red ginseng (*Panax ginseng* Meyer): history, preparation method, and chemical composition. J Ginseng Res 2015;39:384–91.
[3] Hussain A, Bose S, Wang JH, Yadav MK, Mahajan GB, Kim H. Fermentation, a feasible strategy for enhancing bioactivity of herbal medicines. Food Res Inter 2016;81:1–16.
[4] Lee SH, Oh M, Park J, Jang SY, Cheong SH, Lee H, Moon SH. Antioxidant and anti-inflammatory activities of the ethanolic extract of fermented red ginseng marc. Food Sci Biotechnol 2015;24:651–7.
[5] Li Z, Ahn HJ, Kim NY, Lee YN, Ji GE. Korean ginseng berry fermented by mycotoxin non-producing A*spergillus Niger* and A*spergillus oryzae:* ginsenoside analyses and anti-proliferative activities. Biol Pharm Bull 2016;39:1461–7.
[6] Fatima N, Muhammad SA, Khan I, Qazi MA, Shahzadi I, Mumtaz A, Hashmi MA, Khan AK, Ismail T. *Chaetomium* endophytes: a repository of pharmacologically active metabolites. Acta Physiol Plant 2016;38:136.
[7] Zhou ZF, Menna M, Cai YS, Guo YW. Polyacetylenes of marine origin: chemistry and bioactivity. Chem Rev 2015;115:1543–96.

[8] Negri R. Polyacetylenes from terrestrial plants and fungi: recent phytochemical and biological advances. Fitoterapia 2015;106:92–109.
[9] Satoh M, Ishii M, Watanabe M, Isobe K, Uchiyama T, Fujimoto Y. Absolute structure of panaxytriol. Chem Pharm Bull 2002;50:126–8.
[10] Chou TC, Dong HJ, Zhang XG, Lei XG, Hartung J, Zhang YD, Lee JH, Wilson RM, Danishefsky SJ. Multifaceted cytoprotection by synthetic polyacetylenes inspired by the ginseng-derived natural product, panaxytriol. Proc Natl Acad Sci USA 2011;108:14336–41.
[11] Swizdor A. Baeyer-Villiger oxidation of some C_{19} steroids by *Penicillium lanosocoeruleum*. Molecules 2013;18:13812–22.
[12] Rieser MJ, Kozlowski JF, Wood KV, McLaughlin JL. Muricatacin : a simple biologically active acetogenin derivative from the seeds of *Annona muricata* (Annonaceae). Tetrahedron Lett 1991;32:1137–40.
[13] Gurjar MK, Kumar VS, Rao BV. Synthesis of a new type of antitumour agent panaxytriol: synthesis of its four diastereomers. Tetrahedron 1999;55:12563–76.
[14] Winter JM, Cascio D, Dietrich D, Sato M, Watanabe K, Sawaya MR, Vederas JC, Tang Y. Biochemical and structural basis for controlling chemical modularity in fungal polyketide biosynthesis. J Am Chem Soc 2015;137:9885–93.
[15] Yasuhide M, Yamada T, Numata A, Tanaka R. Chaetomugilins, new selectively cytotoxic metabolites, produced by a marine fish-derived *Chaetomium* species. J Antibiot 2008;61:615–22.
[16] Tao SJ, Wang Y, Zhang X, Guan SH, Guo DA. Biotransformation of gambogenic acid by *Chaetomium globosum* CICC 2445. Nat Prod Comm 2012;7:197–8.
[17] Dong XR, Gao ZH, Hu HX, Gao RR, Sun D. Microbial transformation of pseudoprotodioscin by *Chaetomium olivaceum*. J Mol Catal B: Enzym 2016;130:88–95.