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Antifungal metabolite profiling in *Chaetomium globosum* potential strain Cg2 effective against *Bipolaris sorokiniana*

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ABSTRACT

The fungus reported to be a potential antagonist of various soil and seed borne plant pathogens. *C. globosum* mycoparasitizes and produce antifungal metabolites which suppress the growth of the pathogenic fungi. Despite sufficient knowledge available on secondary metabolites of *C. globosum* and their wide biological activities, limited literatures are available on the polar active constituents and their potential use as antifungal agent. The study was carried out to evaluate chemical composition of secondary metabolites from *C. globosum* when it interacts with *Bipolaris sorokiniana* (2017-2020). The volatile compounds identified through GC-MS revealed that, *C. globosum* strain Cg2 produced a variety of antifungal secondary metabolites, i.e. octadecene trans-limonene oxide, dodecane, tetracosonal, heptacosanol and octadecanoic acid which may be involved in the antagonism. Similarly, UPLC-QToF-ESIMS analysis of chloroform soluble fraction of *C. globosum* (Cg2), *B. sorokiniana* (BS112) and their interaction (Cg2-BS112) were undertaken to identify non-volatile metabolites.These metabolites were identified as Chaetomugilin A, D, E, F, Globoxanthone A, Chaetoviridin A, B, E, Chaetoglobin B, Chaetoquadrin A, Chaetocochin B and F, Chaetoglobosin Q and N.The work indicates that the biocontrol agent *C. globosum* showed high antifungal metabolite production thereby antagonising *B. sorokininana* pathogen. The obtained data will greatly enrich current *C. globosum* metabolomic information and provide a good foundation for better understanding of biocontrol mechanism of *C. globosum* against plant pathogens and facilitating widespread application in the field of bio-control.

Keywords: *Bipolaris sorokiniana,* Biocontrol mechanism, Metabolites

The endophytic fungus *Chaetomium globosum* (Phylum-Ascomycota) has got international recognition due to its potential biocontrol activity and high adaptability to various ecological conditions. The fungus is well-known mesophilic member of the family Chaetomiaceae established by Kunze in 1817 (Von *et al*. 1986). It produces lemon-shaped ascospores in globose to pyriform shaped perithecia clothed with irregularly coiled appendages (Domsch *et al*. 1993). There are multiple reports which illustrate the potential of *C. globosum* as a biocontrol agent. *C. globosum* induces pathogen inhibition by secreting secondary metabolites. To date, more than 200 compounds have been reported from this genus (Zhang *et al*. 2013). Different *Chaetomium* species secrete different substances associated with unique and diverse structural types, such as chaetoglobosins, azaphilones, xanthones, anthraquinones, terpenoids, and steroids etc (Zhang *et al*. 2013). It has been reported to produces a variety of antifungal metabolites such as chaetoglobosins A & C, cochliodinol, chaetomugilin A&D, and prenisatin (Mandal *et al*. 1999, Qin *et al*. 2009, Aggarwal *et al*. 2013) which suppress the growth of many soil and seed-borne phytopathogens such as *Pythium ultimum, Phytopthora citrophtora, Alternaria, Fusarium* spp*., Bipolaris sorokiniana* and *Rhizoctonia solani* (Soytong *et al*. 2001, Jiang *et al*. 2017).

C. globosum isolate Cg2 was identified as a potential biocontrol agent against spot blotch pathogen *B. sorokiniana* in earlier studies (Mandal *et al*. 1999, Biswas *et al*. 2000, Rajkumar *et al*. 2005). In this study we unravelled the biocontrol mechanism to report its probable role in antagonism against *B. sorokiniana* isolate BS112 using RNA-seq (Darshan *et al*. 2020). Limited literature is available on chemo-profiling of volatile and non-volatile secondary metabolites of *C. globosum*. Preliminary investigations are being made only to identify certain metabolites and their other biological activities (Sharma *et al*. 2014).To improve efficacy of biological control, however, detail understanding of possible mechanism of action of bioactive metabolites is needed. Therefore, the present work was undertaken to characterize the bioactive secondary metabolites of *C.*

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globosum Cg2 during its different stages of interaction with phytopathogenic fungus *B. sorokiniana*.This data provides a good foundation for continued researches into *C. globosum* Cg2 for facilitating widespread application in the field of agricultural bio-control.

MATERIALS AND METHODS

Experimental materials: *Chaetomium globosum* Cg2 (Accession number AY429049) was used as the antagonistic fungus which was isolated earlier from wheat leaf surface (Mandal *et al*. 1999) and *Bipolaris sorokiniana* BS112 (Accession number KU201275) previously characterized as a highly virulent isolate of the pathogen causing spot blotch in wheat plants (Aggarwal *et al*. 2010) was used as target pathogen. The present research work was carried out at Fungal Molecular Biology Laboratory, Division of Plant Pathology, ICAR-Indian Agricultural Research Institute, New Delhi, during 2017-20. The strains were grown in potato dextrose agar (PDA) medium at 25±2°C. The pure cultures of the fungi were obtained by single spore isolation and the cultures were maintained on PDA slants at 25±2°C with periodic sub culturing for further studies.

Extraction of crude metabolites: In order to explore the full biosynthetic potential of *C. globosum* Cg2, the secondary metabolites profile was examined. A virulent strain (BS112) of *B. sorokiniana* (Aggarwal *et al*. 2008) was mass cultured and crude extracts were obtained by following chloroform solvent extraction protocol described by Aggarwal *et al*. (2011) with slight modifications using rotary evaporator (55°C and 120 rpm). The crude extracts of BS112 @1000 ppm were transferred aseptically to the conical flask containing 100 mL of potato–dextrose broth (PDB) (Fig 1). Subsequently, two agar plugs from actively growing colony of *C. globosum* were transferred aseptically into conical flask. The control was the PDB flask containing only a *C. globosum* mycelia disc and the crude extracts of BS112. The flasks were incubated at 25±2°C for 15 days. The crude metabolites were extracted from culture filtrate by separating funnel using chloroform as solvent. The chloroform layer was collected and the solvent was completely evaporated. The extracts were concentrated by using rotary evaporator (55°C and 120 rpm). The extraction procedures were performed in triplicates. The concentrated crude extracts (oily residue) were then dissolved in 1 ml methanol in small glass vials and kept for drying at room temperature. The dried powder was diluted with 1 ml chloroform and used for further GC-MS/ LC-MS analysis.

GC-MS analysis of crude metabolites for identification of volatile antifungal compounds: To unravel the interaction, further metabolomic profiling was carried out in GCMS-QP-2010 plus system (thermo scientific trace GC ultra DSQ II). RTx-5 Sil MS column (30 m × 0.25 mm id × 0.25 film thickness). The operating conditions of the column were as follows: Oven temperature program from 60-280°C at 4°C/ min withhold time of 3 min and from 250- 280°C at 15°C/ min withhold time of 6 min, and the final temperature was kept for 10 min. The injector temperature was maintained at 270°C, the volume of injected sample was 0.3 µl; pressure 73.3 kPa, total flow 16.3 mL/min, column flow 1.21 mL/ min, linear velocity 40.1 cm/sec, purge flow 3.0 mL/ min, split ratio: 10.0; ion source temperature 230°C; scan mass range of m/z 50-650 and interface line temperature 280°C. The identification of compounds was performed by comparing the mass spectra of sample with data from NIST 11 (National Institute of Standards and Technology, US) data library and WILEY 8 (Senthilkumar *et al*. 2006).

UPLC-QTOF-MS/MS analysis of crude metabolites for identification of non-volatile antifungal compounds: UPLC-QTOF-MS/MS was carried out using an ACQUITY UPLC and SCIEX SelexION Triple QuadTM 5500 System (Waters, USA) equipped with an Acquity BEH C18 column (2.1 × 100 mm, 1.7 µm). Electro-spray Ionization mass (ESI-MS) spectra for crude chloroform extracts of treated samples were measured using a Waters Q-TOF micro-LC–MS/MS instrument (Waters, USA) with Waters Cap-LC system with integrated photodiode array and ESI ion spray source (Jawaharlal Nehru University, New Delhi, India). The UPLC conditions were as follows: the mobile phase consisted of water (eluent A) and 0.1% acetonitrile (eluent B), the column temperature was 45ÊC, the injection volume was 3.00 µL, and the running time was 26.50 min. MS parameters were as follows: the spectrometer was operated in the positive ion mode using an electrospray-ionization source, the capillary voltage was 3.0 kV, the sampling cone voltage was 4.0 V, the extraction cone voltage was 3.0 V, the ion source temperature was 105ÊC, the atomization air temperature was 350ÊC, the atomizing gas flow was 700.0 L/h, the collision voltage was 3.0 eV, the scan time was 0.300 s, the scan range was 200±2200 m/z, and LockSpray online correction was performed using 200 ng/ mL leucine enkephalin (556.2771 m/z). The samples were dissolved in MeOH for HPLC (1 mg/ml) for injection into the HPLCESI-MS system. Separation through LC-column was performed using gradient separation from 20 to 100 % acetonitrile/water over a period of 10 min with a flow rate 1 ml/ min, and monitored by absorption at 254 nm with a photodiode array detector. Positive and negative ionization modes were detected with mass scan range 100-1,400 amu. The identification and analysis of compounds was performed by using METLIN batch search with accuracy of 10 ppm (https://xcmsonline.scripps.edu).

RESULTS AND DISCUSSION

Chloroform soluble fraction of BS112 revealed only eight compounds, representing 66.2% of the total extract. Hydrocarbons such as octahydro-naphthalen (19.7%) and pyrene (14.7%) were found to be the major constituents of the extract. Nonadienone (16.2%) was also found to be abundant. While, chloroform extract of Cg2 subjected to GC-MS analysis, showed nine volatile organic compounds, accounting 63.9% of the extract. The extract has been found dominated with octadecene (20.2%) followed by pyrene hydrocarbon (13.8%), hexadecene (9.7%) and octahydro-naphthalen (8.7%). Total 13 compounds were identified

from the total ion chromatogram of Cg2-BS112 interaction culture, contributing 85.8% of the chloroform extract. Among these, octadecene (24.9%) and trans-limonene oxide (21.8%) were found to be the most abundant followed by tetradecene (7.2%), heptacosonal (6.9%), tetracosonal (6.6%), octadecanoic acid (5.2%), dodecene (4.4%), cyclohexadiene (4.3%) and hexadecene (3.9%). Besides, minor components were also identified as hexadacane (2.1%), methyl butenol (1.9%) and nonadienone (1.8%). All the identified compounds were grouped into their chemical classes which showed highest content of oxygenated derivatives (44.2%). Among the oxygenated derivatives, ketones (23.5%) contributed maximum followed by alcohols (15.5%) and acids (5.2%) (Table 1). In another experiment valeric acid methyl ester and butane-diol were identified from GC-MS analysis of an endophytic *Chaetomium* sp. (Guo *et al*. 2008).

UPLC-QToF-ESIMS analysis of chloroform soluble fraction of C. globosum (Cg2) exposed to Bipolaris sorokiniana (BS112) crude toxin: Analysis of chloroform extract of Cg2 culture resulted in tentative identification of 18 secondary metabolites. These metabolites were identified based on their molecular ion peaks, adduct ion peaks and matching with their available literature reports. These metabolites were characterized as Chaetomugilin A, D, E, F, *Chaetocromone A,* Globoxanthone A, Chaetoviridin A, B, E, Chaetoglobin B, Chaetoquadrin A, Rotiorinol B, Chaetomin, Chaetocochin B and F, Xanthoquinodin A1, Chaetoglobosin Q and N (Fig 1, 2). Likewise, these metabolites were also identified based on their molecular ion, adduct ion and sodiated ion peaks (Table 2). The occurrence of chaetomugilins were reported in *C. globosum* (Muroga *et al*. 2010). Chaetomin was known to be produced by *C. globosum* and *C. cochliodes* (Safe and Taylor 1972). Another study by Yu *et al*. (2018) reported chaetomin and cochliodinol as major component produced by both the species of *Chaetomium.* Polyketide derivatives such as chaetoquadrins have been known to be produced by *C. gracile* (Bai *et al*. 2015).

It was imperative to investigate the secondary metabolites produced by these two fungi during interaction in the same culture medium. Thus, the metabolites were extracted following similar process in the combination culture, Cg2-BS112 and analysed in UPLC-QToF-ESIMS (Fig 1). Various peaks corresponding to their major metabolites were detected in the total ion chromatogram. Among these total seven metabolites were identified based on the adduct ion peaks which are matching with their exact neutral molecular mass. These secondary metabolites were identified as methyl-benzoquinone, epichaetoviridin A, globoxanthone A, chaetoviridin E, secoclavine, bipolaroxin and victoxinine (Table 2).Wang *et al*. (2017) reported the presence of azaphilones, mainly chaetoviridins A-C, E and chaetomugilin D in *Chaetomium* sp. NA-SOI-R1. Chaetoviridin E and F along with chaetochalasan A were identified in *C. globosum* which showed tremendous antibiosis in biological control of spot blotch of wheat

Table 1 GC-MS profile showing different volatile compounds during Cg2*BS112 interaction

Chemical compound	BS112 control		Cg2 control		Cg2 *BS112	
	RT	(Area %)	RT	(Area %)	RT	(Area %)
Octahydro-naphthalen	17.86	19.65	17.84	8.66	17.83	5.53
Nona-dienone	17.92	16.22	17.91	2.03	17.91	1.77
Octadecene	19.05	1.76	19.05	20.2	19.05	14.04
Butylphenol	13.83	2.37	-	0.70	-	-
Pyrene	20.53	14.72	-	13.83	-	-
Acetic acid	17.62	2.40	-	-	-	-
Hexadecenal	14.77	3.50	-	-	-	-
Norusa-dienone	17.92	7.65	-	-	-	-
Pregnane	17.70	10.50	-	-	-	-
Lumisantonin	21.92	0.45	-	-	-	-
Mepivacaine	24.75	0.28	-	-	-	-
Hexadecene	-	-	14.78	9.69	14.76	3.93
Hexadacane	-	-	14.85	4.16	14.85	2.21
Tetracosanol	-	-	20.91	2.89	20.91	6.61
Methyl butenol	-	-	18.11	1.73	18.11	1.93
trans-Limonene oxide	-	-	-	-	16.11	21.75
Dodecene	-	-	-	-	9.362	4.43
Tetradecene	-	-	-	-	12.24	7.23
Cyclohexa-diene	-	-	-	-	13.22	4.25
Heptacosanol	-	-	-	-	22.68	6.92
Octadecanoic acid	-	-	-	-	20.06	5.20
Total	79.5		63.89		85.8	
Chemical group			*Content (%)*			
Hydrocarbons	46.91		56.54		41.62	
Alkanes	30.15		12.82		7.74	
Alkenes	16.76		43.72		33.88	
Ketones	24.32		2.03		23.52	
Alcohols	2.37		5.32		15.46	
Aldehydes	3.50		-		-	
Acid	2.40		-		5.20	
	79.5		63.89		85.8	

Table 2 UPLC-QTOF-MS/MS analysis and tentative identification of secondary metabolites in *C. globosum* Cg2* *B. sorokiniana* BS112 interaction

Tentative Compound	Molecular formula	Neutral mass (Da)	Observed m/z	Adduct
C. globosum				
Chaetomugilin E	$C_{24}H_{29}ClO_6$	447.1915	448.1921	H^+
Chaetomugilin A	$C_{23}H_{27}ClO_7$	450.1689	451.1682	H^+
Chaetomugilin F	$C_{23}H_{25}ClO_5$	418.1481	418.1463	H^+
Chaetomugilin D	$C_{23}H_{27}ClO_6$	434.2051	457.3984	Na^+
Chaetocromone A	$C_{13}H_{12}O_6$	287.0528	264.0511	Na^+
Globoxanthone A	$C_{15}H_{12}O_7$	303.2999	304.2978	H^+
Chaetoviridin A	$C_{23}H_{25}ClO_6$	432.1876	433.1841	H^+
Chaetoviridin B	$C_{23}H_{27}ClO_6$	434.1496	435.1505	H^+
Chaetoviridin E	$C_{23}H_{23}ClO_5$	413.3087	413.3128, 414.3174	H^+
Chaetoquadrin A	$C_{20}H_{24}O_6$	360.1772	393.1757	Na^+
Rotiorinol B	C23H26O6	398.2084	399.2100	H^+
Chaetomin	$C_{31}H_{26}N_6O_6S_4$	706.6632	706.6656	H^+
Chaetocochin B	$C_{34}H_{34}N_6O_6S_5$	780.2184	781.8427	H^+
Chaetoglobosin Q	$C_{32}H_{38}N_2O_6$	545.5821	546.5926	H^+
Chaetoglobosin N	$C_{33}H_{38}N_2O_5$	542.2316	543.2668	H^+
Xanthoquinodin A1	$C_{31}H_{24}O_{11}$	595.5160	595.5134	H^+
Chaetocochin F	$C_{33}H_{36}N_6O_6S_5$	772.1721	773.5774	H^+
Chaetoglobin B	$C_{36}H_{44}N_2O_{10}$	664.1012	664.6068	H^+
B. sorokiniana				
Bipolaroxin	$C_{15}H_{18}O_4$	263.2074	264.2165, 264.2182	H^+
Bipolaricin E	$C_{25}H_{40}O_3$	411.2869	411.2821	H^+
Bipolaricin I	$C_{25}H_{35}O_5$	415.2479	415.2479, 437.2905	H^+, Na^+
Versicolorin C	$C_{18}H_{12}O_7$	340.2841	700.2940	H^+, dimer
Prehelminthosporol	$C_{15}H_{22}O_2$	234.1819	235.1906	H^+
Sorokianin	$C_{18}H_{28}O_4$	308.2240	309.2319	H^+
Victoxinine	$C_{17}H_{29}NO$	261.1367	262.1995	H^+
Bipolenin K	$C_{15}H_{22}O_3$	251.1558	251.1646, 499.4698	H^+, dimer
Bipolenin A	$C_{15}H_{28}O_3$	256.2291	514.4673	H^+
Trticone B/ Sporostaphylotrichin B	$C_{14}H_{15}NO_5$	277.2309	278.1995, 577.2101	H^+, Na^+ dimer
Spirostaphylotrichin A	$C_{14}H_{17}NO_5$	279.2911	280.2149	H^+
Spirostaphylotrichin D	$C_{14}H_{15}NO_5$	277.2309	278.1982, 278.1989	H^+
Spirostaphylotrichin E/R	$C_{14}H_{17}NO_5$	279.2911	280.2162, 280.2155	H^+
Spirostaphylotrichin R/E	$C_{14}H_{17}NO_5$	279.2911	280.2149	H^+
*C. globosum Cg2*B. sorokiniana BS112 crude extracts*				
Epichaetoviridin A*	$C_{23}H_{24}ClO_6$	431.0125	431.9526	H+
Globoxanthone A*	$C_{15}H_{12}O_7$	303.2999	304.2978	H^+
Chaetoviridin E	$C_{23}H_{25}ClO_6$	432.1876	433.1841	H^+
Secoclavine*	$C_{14}H_{14}N_2$	210.2921	211.2714	H^+
Bipolaroxin	C15H18O4	263.2074	264.2165	H^+
Victoxinine	$C_{17}H_{29}NO$	261.1367	262.1995	H^+
Methyl-benzoquinone*	$C_7H_5O_2$	121.0334	121.8928	H^+

*Metabolite produced only in interaction of *C. globosum* Cg2 with *B. sorokininana* BS112 crude extracts

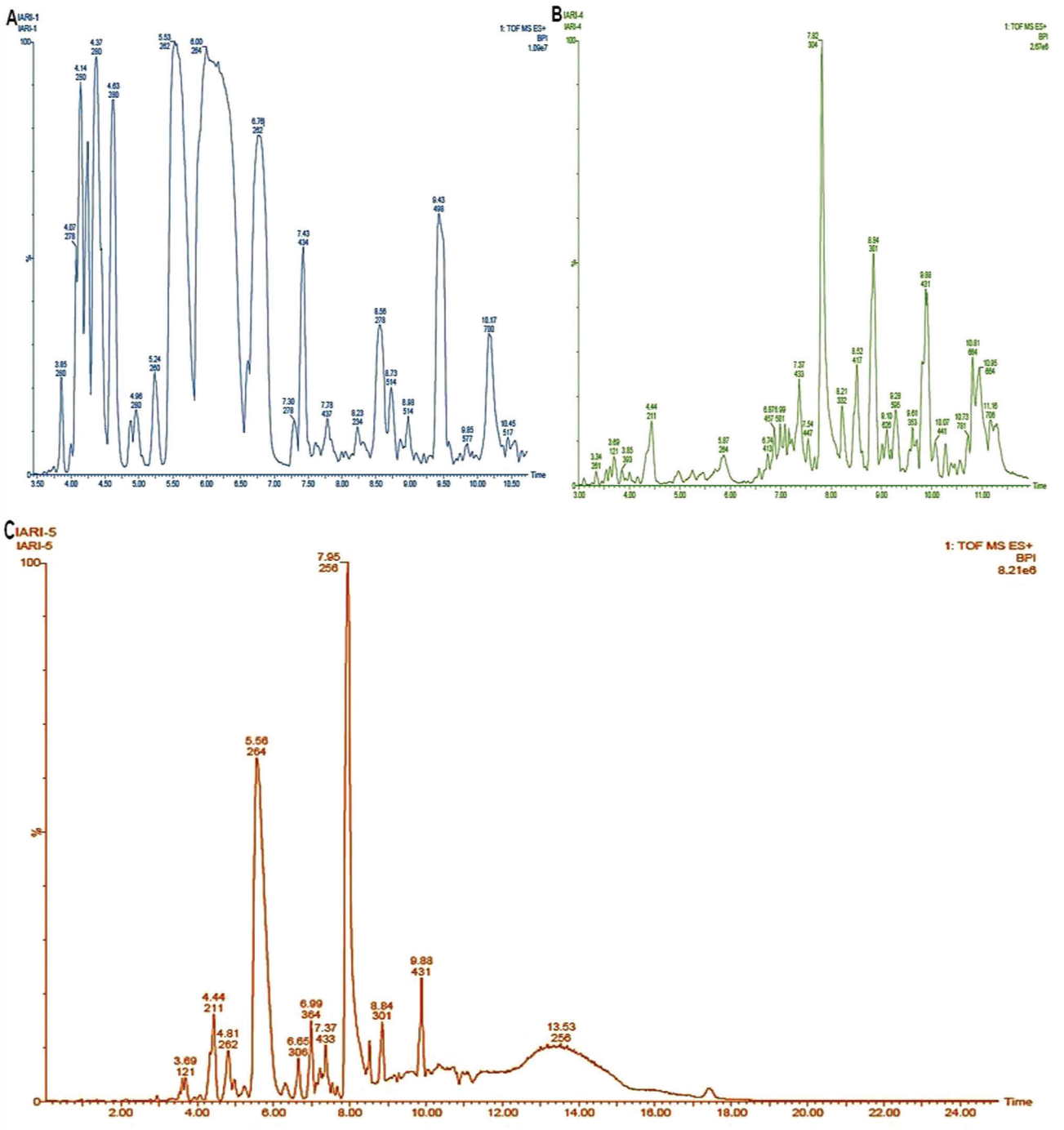

Fig 1 UPLC-QTOF-MS/MS Chromatogram showing different non-volatile compounds during interaction of *Chaetomium globosum* (Cg2) with *Bipolaris sorokiniana* (BS112) crude extracts. A) *B. sorokiniana* (BS112) Control; B) *C. globosum* (Cg2) Control; C) *C. globosum* (Cg2) +*B. sorokiniana* (BS112) crude extracts.

caused by *C. sativus* (Pornsuriya and Soytong 2008). Chaetoglobosins has been isolated and characterized by various researchers due its strong inhibitory activity. In the present study, chaetoglobosin analogous such as chaetoglobosin Q and N were identified. These data provide a good foundation for continued researches into *C. globosum* Cg2 for facilitating widespread application in the field of agricultural bio-control.

Chaetomium genus of kingdom fungi is considered to be a rich source of unique bioactive metabolites. In recent years, biological control of soil borne pathogen has received increasing attention as a promising candidate or alternative option to chemical control. *Chaetomium globosum* mycoparasitizes the pathogen and produce antifungal metabolites which suppress the growth of the pathogenic fungi. In the present study, GC-MS analysis showed that *C. globosum* strain Cg2 produces variety of antifungal secondary metabolites such as trans-limonene

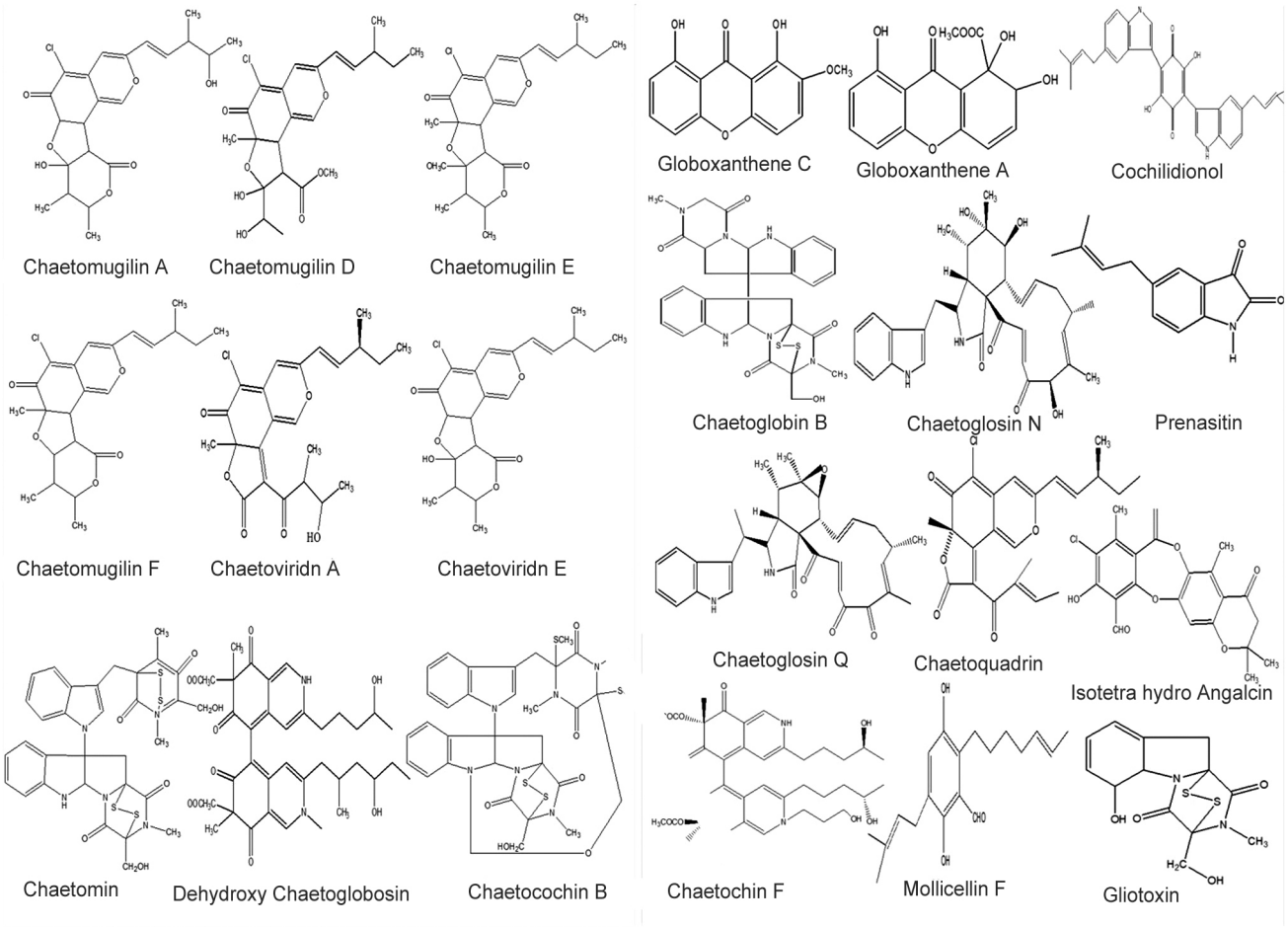

Fig 2 Secondary metabolites identified in chloroform extracts of *C. globosum* (Cg2).

oxide, dodecene, tetradecene, cyclohexadiene, heptacosanol and octadecanoic acid which may be involved in the antagonisms. Similarly, UPLC-QToF-ESIMS analysis showed that epichaetoviridin A, globoxanthone A, chaetoviridin A, B, E and chaetomin were produced by *C. globosum*. In conclusion, *C. globosum* can be used as a nonchemical alternative treatment for the biological control of spot blotch of wheat and other soil borne diseases through production of antifungal metabolites.

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