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REVIEW

Chaetomium endophytes: a repository of pharmacologically active metabolites

Nighat Fatima[1] · Syed Aun Muhammad[2] · Ibrar Khan[3] · Muneer Ahmed Qazi[4] · Irum Shahzadi[5] · Amara Mumtaz[6] · Muhammad Ali Hashmi[6] · Abida Kalsoom Khan[6] · Tariq Ismail[1]

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Abstract Fungal endophytes are group of fungi that grow within the plant tissues without causing immediate signs of disease and are abundant and diverse producers of bioactive secondary metabolites. The *Chaetomium* genus of kingdom fungi is considered to be a rich source of unique bioactive metabolites. These metabolites belong to chemically diverse classes, i.e., chaetoglobosins, xanthones, anthraquinones, chromones, depsidones, terpenoids and steroids. *Cheatomium* through production of diverse metabolites can be considered as a potential source of antitumor, cytotoxic, antimalarial, antibiotic and enzyme inhibitory lead molecules for drug discovery. This review covers isolation of *Cheatomium* endophytes, extraction and isolation of metabolites and their biological activities.

Keywords Endophytes · *Chaetomium* · Drug discovery · Endophytes · Metabolites

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✉ Nighat Fatima
nighatmrl@yahoo.com; nighatfatima@ciit.net.pk

[1] Department of Pharmacy, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan

[2] Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

[3] UNESCO Chinese Center of Marine Biotechnology, Ocean University of China, Qingdao, China

[4] Department of Microbiology, Shah Abdul Latif University, Khairpur, Sindh 66020, Pakistan

[5] Department of Environmental Sciences, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan

[6] Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan

Introduction

Endophytes are the microorganisms, usually becoming a part of plant's life by colonizing in its internal tissues without causing any disease to it (Bacon and White 2000). Endophytes enhance the resistance of their host against pathogenic attack by producing bioactive secondary metabolites so that they can survive in adverse conditions (Azevedo et al. 2000; Strobel 2003). The endophytic fungi play important physiological and ecological (Tintjer and Rudger 2006) roles in their host's life. The existence of these endophytic microorganisms is well established, but their geographical distribution and diversity are unknown (Arnold and Engelbrecht 2007). Medicinal plants harbor endophytic fungi and are considered to be able to produce pharmaceutically important products (Zhang et al. 2006). Therefore, nowadays endophytic mycoflora of medicinal plant is considered as a new domain to be explored.

Recent development in screening technologies portrays that endophytic microorganisms are an untapped source of chemically and biologically diverse metabolites (Zhang et al. 2012; Aly et al. 2010). In addition, natural products from endophytic fungi with unique chemical structures indicate emergence of chimeric metabolic machinery of these microorganisms (Gunatilaka 2006). Approximately, 1.5 million fungal species are present on earth but very few ($\approx$7 %) have been studied until now (Aly et al. 2010). More than 300 natural products have been isolated from endophytes between 1987 and 2006 (Zhang et al. 2006).

Chaetomium is one of the large genera of *Chaetomiaceae* family which contains more than 100 species. *Chaetomium* genus has been reported as a rich source of unique natural products. A large number of unique and structurally diverse classes of compounds such as azaphilones, terpenoids, steroids, chaetoglobosins, xanthones,

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chromones, epipolythiodioxopiperazines, depsidones and anthraquinones have been reported from *Chaetomium* species. These compounds, because of their chemical diversity, showed significant biological activities, such as enzyme inhibitory, cytotoxic, antitumor, antimalarial and antibiotic (Zhang et al. 2012). In current review, we have covered in detail the isolation of *Chaetomium* endophytes, metabolites and their biological activities.

Taxonomy and morphological features

Taxonomy

Kingdom: Fungi
Order: Sordariales
Phylum: Ascomycota
Family: Chaetomiaceae
Class: Euascomycetes
Genus: *Cheatomium*

The genus *Chaetomium* comprises more than 100 species (Von Arx et al. 1986). *Chaetomium globosum* (*C. globosum*) is the well-known and studied species of this genus; other species include *C. funicola*, *C. atrobrunneum* and *C. strumarium.*

Habitat/ecology

Chaetomium is a common fungal genus with a worldwide ubiquitous distribution and is widespread in soil and on decaying plant materials, but spore concentrations in outdoor air are not very high (Abbott et al. 1995). *Chaetomium* is also found indoors on a variety of substrates containing cellulose, including document archives, wallpaper, textiles and construction materials (Samson et al. 1984). Some species of this genus are also found as endophytes, live mutually in healthy plants (Zhang et al. 2012).

Growth requirements

Some *Chaetomium* species grow well between 16 and 25 °C but most species need temperature range of 25 and 35 °C. Few species are thermotolerant or thermophilic (Von Arx et al. 1986). These species grow well between 35 and 37 °C and are reported to cause human diseases (Barron et al. 2003). Several groups of *Chaetomium*: mesophilic (15–35 °C), semi-mesophilic (15–37 °C), microthermophilic (15–40 °C), thermotolerant (15–45 °C) and thermophilic (25–55 °C) can be distinguished on the basis of optimal growth temperature and medium used for fermentation (Millner 1977).

Isolation of *Chaetomium* endophytes and their host plants

Isolation of endophytes is a critically important step to determine the maximum number of colonized endophytes and hence there is a need to eradicate epiphytic microbes. Various plant parts such as leaves, stems and seeds can be used to isolate endophytes. To minimize or prevent the isolation of pathogenic and saprobic species, the collected plants for studying endophytic communities should be healthy and diseases free (Strobel and Daisy 2003). Numerous methods are described in the literature for isolation of endophytes. A convenient and commonly established method by several researchers is to immerse the tissues in 70 % alcohol for few seconds or in sodium hypochlorite (0.5–3.5 %) for 1–2 min. In case of any of above methods, plant material should be rinsed with sterile double distilled water before inoculating it on the medium (Strobel and Daisy 2003). Water agar, Yeast extract agar, Potato dextrose agar, Rose bengal chloramphenicol agar, Humic acid vitamin agar and Luria–bertani agar are found to be appropriate media for isolation of endophytic fungi, whereas the most suitable temperature for their growth ranges between 25 and 30 °C (Jalgaonwala et al. 2011).

The endophytic strains of *C. globosum* were isolated from *Ephedra fasciculata* and from bark and twigs of *Crataeva magna* (Bharat et al. 2005; Nalini et al. 2005). Some endophytic *Chaetomium* species were also isolated from *Populus tomentosa* and *Aspidosperma tomentosum* (Gao et al. 2005; Rodrigues et al. 2005). The literature survey also revealed the isolation of *Chaetomium* species from leaves and stem of *Adenophora axilliflora* and *Imperata cylindrica* (Jiao et al. 2006; Ding et al. 2006) (Table 1). *Chaetomium* species were also isolated from bark of *Aegle marmelos*, leaves and stem of *Nerium oleander* and roots of *Avocado* (Gond et al. 2007; Huang et al. 2007a; Violi et al. 2007).

The isolation of *C. globosum* was also manifested from leaves of *Viguiera robusta* and *Glinus lotoides* (Momesso et al. 2008; El-Zayat 2008). *Chaetomium* species were isolated from inner bark of *Prosopis cineraria*, *Scapania verrucosa* and leaves of *Acalypha indica* (Gehlot et al. 2008; Guo et al. 2008; Gangadevi et al. 2008). In 2009, many scientists worked on the isolation of endophytes. *Chaetomium* species were also isolated from *Aloe vera*, *Mentha viridis*, *Oryza sativa*, *Ginkgo biloba*, *Salvia officinalis* and *Otanthus maritimus* (Table 1). *C. globosum* QEN-14 was an endophytic fungus isolated from the alga *Ulva pertusa* (Cui et al. 2010). Studies conducted in 2011 showed the isolation of *Chaetomium* species (Table 1) from various plants such as leaves of *V. robusta*, *Tylophora indica*, root of *Cynodon dactylon* and *G. biloba* (Borges

Table 1 *Chaetomium* endophytes and their host plants

Species	Host plant	References
Chaetomium globosum	*Ephedra fasciculata*	Bharat et al. (2005)
Chaetomium spirale	*Populus tomentosa*	Gao et al. (2005)
Chaetomium sp.	*Crataeva magna*	Nalini et al. (2005)
Chaetomium sp.	*Aspidosperma tomentosum*	Rodrigues et al. (2005)
Chaetomium sp. IFB-E015	*Adenophora axilliflora*	Jiao et al. (2006)
Chaetomium globosum IFB-E019	*Imperata cylindrica*	Ding et al. (2006)
Chaetomium globosum NC-1 and CB-3	Wheat	Istifadah and McGee (2006)
Chaetomium globosum	*Aegle marmelos*	Gond et al. (2007)
Chaetomium globosum	Plants of Tucson, Arizona, USA	Yang et al. (2006, 2007)
Cheatomium sp.	*Dactylis glomerata*	Márquez et al. (2007)
Cheatomium sp.	*Nerium oleander*	Huang et al. (2007a, b)
Chaetomium elatum	*Avacado*	Violi et al. (2007)
Cheatomium sp.	Driftwoods in Yellow Sea	Li et al. (2008)
Cheatomium sp.	Shrubs of Southern India	Naik et al. (2008)
Chaetomium globosum	*Viguiera robusta*	Momesso et al. (2008)
Chaetomium globosum	*Glinus lotoides*	El-Zayat (2008)
Chaetomium globosum	Herbaceous plants Southern India	Krishnamurthy et al. (2008)
Chaetomium sp.	*Prosopis cineraria*	Gehlot et al. (2008)
Chaetomium fusiforme	*Scapania verrucosa*	Guo et al. (2008)
Chaetomium sp.	*Acalypha indica*	Gangadevi et al. (2008)
Chaetomium globosum ZY-22	*Ginkgo biloba*	Qin et al. (2009a, b, c)
Chaetomium globossum	Trees of Southern India	Krishnamurthy et al. (2009)
Chaetomium globosum	*Dysosma pleiantha*	Lu et al. (2009)
Chaetomium murorum H12	*Eulophia flava*	Qiu et al. (2009)
Chaetomium globosum H43		
Chaetomium sp.	*Aloe vera* and *Mentha viridis*	Sagar and Thakur (2009)
Chaetomium sp.	*Canavalia cathatica*	Anita and Sridhar (2009)
Chaetomium sp.	*Oryza sativa*	Naik et al. (2009)
Chaetomium sp.	*Salvia officinalis*	Debbab et al. (2009)
Chaetomium sp.	*Otanthus maritimus*	Aly et al. (2009)
Chaetomium globosum QEN-14	*Ulva pertusa*	Cui et al. (2010)
Chaetomium sp. (NIOCC 36)	Mangrove	Ravindran et al. (2010)
Chaetomium globosum	Grasses of Southern India	Shankar and Shashikala (2010)
Chaetomium sp.	*Populus tremula*	Albrectsen et al. (2010)
Chaetomium cupreum	*Macleaya cordata*	Mao et al. (2010)
Chaetomium globosum	*Hyoscyamus muticus*	Abdel-Motaal et al. (2010)
Chaetomium bostrycodes	*Withania somnifera*	Khan et al. (2010)
Chaetomium sp.	*Taxus baccata*	Tayung and Jha (2010)
Chaetomium indicum	*Leucas aspera*	Rajagopal et al. (2010)
Chaetomium globosum	*Ocimum sanctum*, *Tridax procumbens* and *Leucas aspera*	Rajagopal et al. (2010)
Chaetomium globosum	*Viguiera robusta*	Borges et al. (2011)
Chaetomium sp.	*Tylophora indica*	Kumar et al. (2011)
Chaetomium globosum IFB-E036	*Cynodon dactylon*	Ge et al. (2011)
Chaetomium globosum	*Ginkgo biloba*	Li et al. (2011)
Chaetomium sp.	Wheat and barley	Asgari and Zare (2011)
Chaetomium atrobrunneum	*Michaelia champaca*	Srimathi et al. (2011)
Chaetomium sp.	*Prunus avium*	Neda et al. (2011)
Chaetomium globosum L18	*Curcuma wenyujin*	Wang et al. (2012)

Table 1 continued

Species	Host plant	References
Chaetomium globosum	*Vitis vinifera*	Nunez-Trujillo et al. (2012)
Chaetomium fusiforme	*Scapania verrucosa*	Peng et al. (2012)
Chaetomium globosum	*Althaea rosea*	Alhamed and Shebany (2012)
*Chaetomium globosum*LK4	*Capsicum annum*	Khan et al. (2012)
Chaetomium sp.	*Citrus sinensis*	Ho et al. (2012)
Chaetomium globosum	*Gloriosa superba*	Budhiraja et al. (2012)
Chaetomium sp.	*Jatropha curcas*	Kumar and Kaushik (2013)
Chaetomium jatrophae	*Jatropha podagrica*	Sharma et al. (2013)
Chaetomium sp.	Soybean	Leite et al. (2013)
Chaetomium sp.	*Triticum durum*	Sadrati et al. (2013)
Chaetomium sp.	*Bauhinia vahlii*	Bagchi and Banerjee (2013)
Chaetomium globosum CDW7	*Ginkgo bioloba*	Ye et al. (2013)
Chaetomium globosum (GQ 365152, EF 151445)	*Gloriosa superba*	Budhiraja et al. (2013)
Chaetomium sp.	*Bulbophullum neilgherrense* and *Pholidota pallida*	Sawmya et al. (2013)
Chaetomum globossum	*Withania somnifera*	Kumar et al. (2013)
Chaetomium sp.	*Scapania verrucosa*	Wu et al. (2013)
Chaetomium sp.	*Butea monosperma*	Tuppad and Shishupala (2013)
Chaetomium sp.	*Zanthoxylum leprieurii*	Talontsi et al. (2013)
Chaetomium globosum No. 04	*Ginkgo biloba*	Zhang et al. (2013a, b)
Chaetomium globosum	*Ginkgo biloba*	Li et al. (2014)
Chaetomium sp.	*Plumeria acuminata* and *Plumeria obtusifolia*	Ramesh and Srinivas (2014)
Cahetomium sp.	*Eugenia jambolana*	Yadav et al. (2014)
Chaetomium globossum JN711454	*Adiantum capillus*	Selim et al. (2014)

et al. 2011; Kumar et al. 2011; Ge et al. 2011; Li et al. 2011).

Chaetomium species were also isolated from *Curcuma wenyujin*, *S. verrucosa and Althaea rosea* (Wang et al. 2012; Peng et al. 2012; Alhamed and Shebany 2012). Kumar and Kaushik (2013) isolated *Chaetomium* from *Jatropha curcas*. Later on, a new endophytic species of *Chaetomium*, *C. jatrophae* was also reported from fruits of *Jatropha podagrica* (Sharma et al. 2013). Table 1 also enlists some of the studies regarding isolation of *Chaetomium* from *Triticum durum*, *G. biloba* and *Bauhinia vahlii* (Sadrati et al. 2013; Ye et al. 2013; Bagchi and Banerjee 2013). Recently, many scientists worked on isolation and characterization of *Chaetomium* species (Li et al. 2014; Selim et al. 2014; Ramesh and Srinivas 2014) (Table 1).

Role of *Chaetomium* endophyte in drug discovery

Fungi are proved to be a rich source of natural products with a variety of therapeutic properties. These secondary metabolites are considerably important as new lead compounds for medicine in pharmaceutical industry as well as for plant protection (Yu et al. 2010). In the last decade, fungi of genus *Chaetomium* have been reported for the production of structurally unique and complex natural products possessing various significant biological activities such as anticancer, cytotoxic, antibiotic, antioxidant, antimalarial and enzyme inhibitory (Zhang et al. 2012).

Anticancer and cytotoxic metabolites

Cancer is a group of diseases characterized by propagation of abnormal cell growth with potential to invade or spread to other parts of body and ultimately leads to death (Pimentel et al. 2010). Recent approaches for treatment of cancer involve combination of radiation therapy, chemotherapy, surgery, monoclonal antibody and immunotherapy therapy. These approaches have numerous side effects, mainly non-specific cytotoxicity of anticancer drugs (Gangadevi and Muthumary 2008). There is a continuous rise in mortality rate of cancer as well as the enormity in spite of availability of various treatment choices. This indicates inadequacy of current therapies and suggests a need to investigate newer sources to obtain more specific approaches to treat cancer. There are many reports about isolation of anticancer and cytotoxic compounds from *Chaetomium* genus.

Cytotoxic cytochalasins

Cytochalasins are considered an important class of cytotoxic fungal metabolites. Cytochalasins have affinity for actin filaments and can block elongation of filaments and polymerization (Udagawa et al. 2000). They can inhibit cellular processes such as cell division, alter cellular morphology and even cause cells to undergo apoptosis. A variety of cytotoxic cytochalasin derivatives: chaetoglobosin, isochaetoglobosins, cytoglobosins and chaetomugilins have been reported from *Chaetomium* species.

Kobayashi et al. reported the isolation of seven chaetoglobosins A–F (**1–6**) and J (**7**) from *Chaetomium* species endophyte of alga *Halimeda discoidea* (Kobayashi et al. 1996). Ni et al. also reported the isolation of compounds **1** and **2** from *C. globosum* Ly50 endophyte of *Maytenus hookeri.* Ding et al. isolated a new cytochalasin, chaetoglobosin U (**8**) together with four known compounds **3**, **5**, **6**, and penochalasin A (**9**) from *C. globosum* IFB-E019 previously isolated from *I. cylindrical* (Fig. 1a). These compounds showed cytotoxic activities against the human nasopharyngeal epidermal tumor KB cell lines with IC_{50} values of 16, 34, 52, 48 and 40 µM, respectively (Ding et al. 2006). In 2008, Memesso et al. (2008) reported chaetoglobosins (**2**, **4** and **5**) from endophytic *C. globosum* strain associated with *V. robusta* and compound **2** showed 89.55 and 57.10 % of inhibition at 0.1 mg ml^{-1} against Jurkat (leukemia) and B16F10 (melanoma) tumoral cells, respectively. Chaetoglobosin A (**1**) and C (**3**) were also isolated from *C. globosum* endophyte of *G. biloba* (Qin et al. 2009a).

Investigation of ethyl acetate extract of another *C. globosum* IFB-E041of *Artemisia annua* led to the isolation of two new chaetoglobosins V (**10**) and W (**11**) along with the known cheatogolobosins A, C, E, F, G (**12**) and F_{ex} (**13**) (Zhang et al. 2010). These chaetoglobosins exhibited significant cytotoxic activities against four human cancer cell lines, K562 (human leukemic cell line), KB (mouth epidermal carcinoma cells), HepG2 (human hepatocellular liver carcinoma cell line) and MCF-7 (breast cancer cell line) with IC_{50} values in a range of 18–30 µg ml^{-1}. Compound **13** along with isocheatoglobosin D (**14**) was also reported from *C. globosum* QEN-14, an endophytic fungus of *U. pertusa* (Cui et al. 2010). Chaetoglobosin Vb (**15**) was isolated from *C. globosum*, an endophyte of *G. biloba* (Xue et al. 2012). Chaetoglobosin X (**16**) was isolated from *C. globosum* L18, an endophyte of *C. wenyujin* that exhibited the strongest cytotoxic activity with IC_{50} values of 3.125 and 6.25 µg ml^{-1} against H22 (hepatic cancer cells in mice) and MFC (gastric cancer cells in mice) cancer cell lines, respectively (Wang et al. 2012).

Chaetoglobosin R (**17**) along with a known compound was also isolated from *C. globosum* No.04 endophyte of *G. biloba* (Zhang et al. 2013a, b). Li et al. evaluated chaetoglobosins for their cytotoxic activities against the HTC116 cell line from previously investigated *Chaetomium* endophyte of *G. biloba* (Li et al. 2014). Chaetoglobosins A, F_{ex} and dihydrochaetoglobosin A (**18**) showed high cytotoxic activity with IC_{50} values of 3.15, 4.43 and 8.44 µM, respectively while other chaetoglobosins were found to be weak (IC_{50} >17 µM) (Fig. 1a). Chaetoglobosins were also reported from ethyl acetate extract of *C. globosum* JN711454, an endophyte of *Adiantum capillus* (Selim et al. 2014). Chaetoglobosin Y (**19**) along with known chaetoglobosins was isolated from the endolichenic fungal strain *C. globosum* (No. 64-5-8-2). These compounds showed cytotoxic activity against human colon carcinoma HCT-116 cell line (Zheng et al. 2014) (Fig. 1b).

Another class of cytochalasins, cytoglobosins also reported from different species of *Chaetomium* exhibited cytotoxic activity. Cytoglobosins A–G (**20–26**) were isolated from *C. globosum* QEN-14 (Fig. 1b). Cytoglobosins C (**22**) and D (**24**) displayed cytotoxic activity against the A-549 tumor cell line with IC_{50} values of 2.26 and 2.55 µM, respectively (Cui et al. 2010). Cytoglobosin B (**21**) and C (**22**) were also isolated from *C. globosum* (No. 64-5-8-2) and compound **22** showed cytotoxicity to HCT-116 cell line with IC_{50} value of 11.32 ± 1.00 µM (Zheng et al. 2014).

Ge et al. reported isolation of alkaloidal azaphilones chaetoglobin A and B (**27–28**) from *C. globosum* IFB-E019, an endophyte of *I. cylindrical* (Ge et al. 2008). Chaetoglobin A (**27**) showed inhibitory effect against human breast cancer cell line MCF-7 and colon cancer cell line SW1116 with their IC_{50} values of 26.8 and 35.4 µg ml^{-1}, respectively.

Another class of cytotoxic metabolites, chlorinated azaphilones chaetomugilins A–**F** (**29–34**) was isolated from *C. globosum* OUPST106B-6, an endophyte of *Mugil cephalus* (Yamada et al. 2008; Yasuhide et al. 2008). Chaetomugilins A (**29**), C (**31**) and F (**34**) showed cytotoxic activity against P388 cell lines, with IC_{50} values of 8.7, 3.6 and 3.3 µg ml^{-1}. These compounds also showed cytotoxic effect against HL-60 (Human promyelocytic leukemia) cell lines and IC_{50} values were 7.3, 2.7 and 1.3 µg ml^{-1}, respectively. Compounds **29** and **32** displayed clear toxicity against brineshrimp and *Mucor miehei* and were also isolated from endophyte *C. globosum* (Fig. 1b).

Chaetomugilins G–O (**35–43**), 11-*epi*chaetomugilin A (**44**), 4-*epi*chaetomugilin A (**45**), seco-chaetomugilins A (**46**) and D (**47**) were obtained from *C. globosum* OUPS-T106B-6. Secochaetomugilin D (**47**) has antiproliferative activity against KB, HL-60, L1210 and P388 cells (Yamada et al. 2009). Four new chaetomugilins P–R (**48–50**) and 11-epi-chaetomugilin I (**51**) were isolated from *C.*

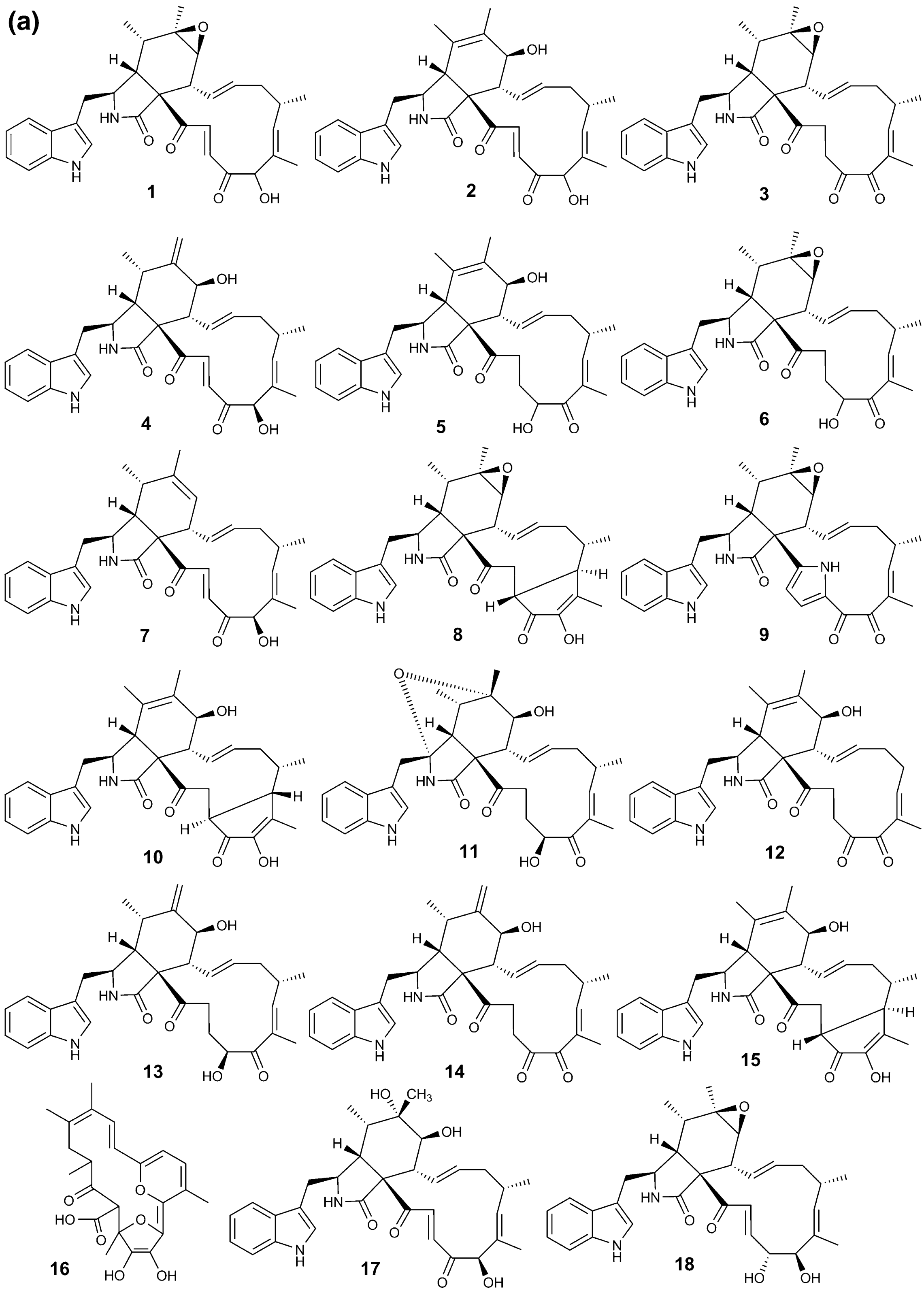

Fig. 1 **a** Anticancer and cytotoxic metabolites from *Cheatomium* endophytes (**1–18**). **b** Anticancer and cytotoxic metabolites from *Cheatomium* endophytes (**19–47**). **c** Anticancer and cytotoxic metabolites from *Cheatomium* endophytes (**48–57**). **d** Anticancer and cytotoxic metabolites from *Cheatomium* endophytes (**58–88**)

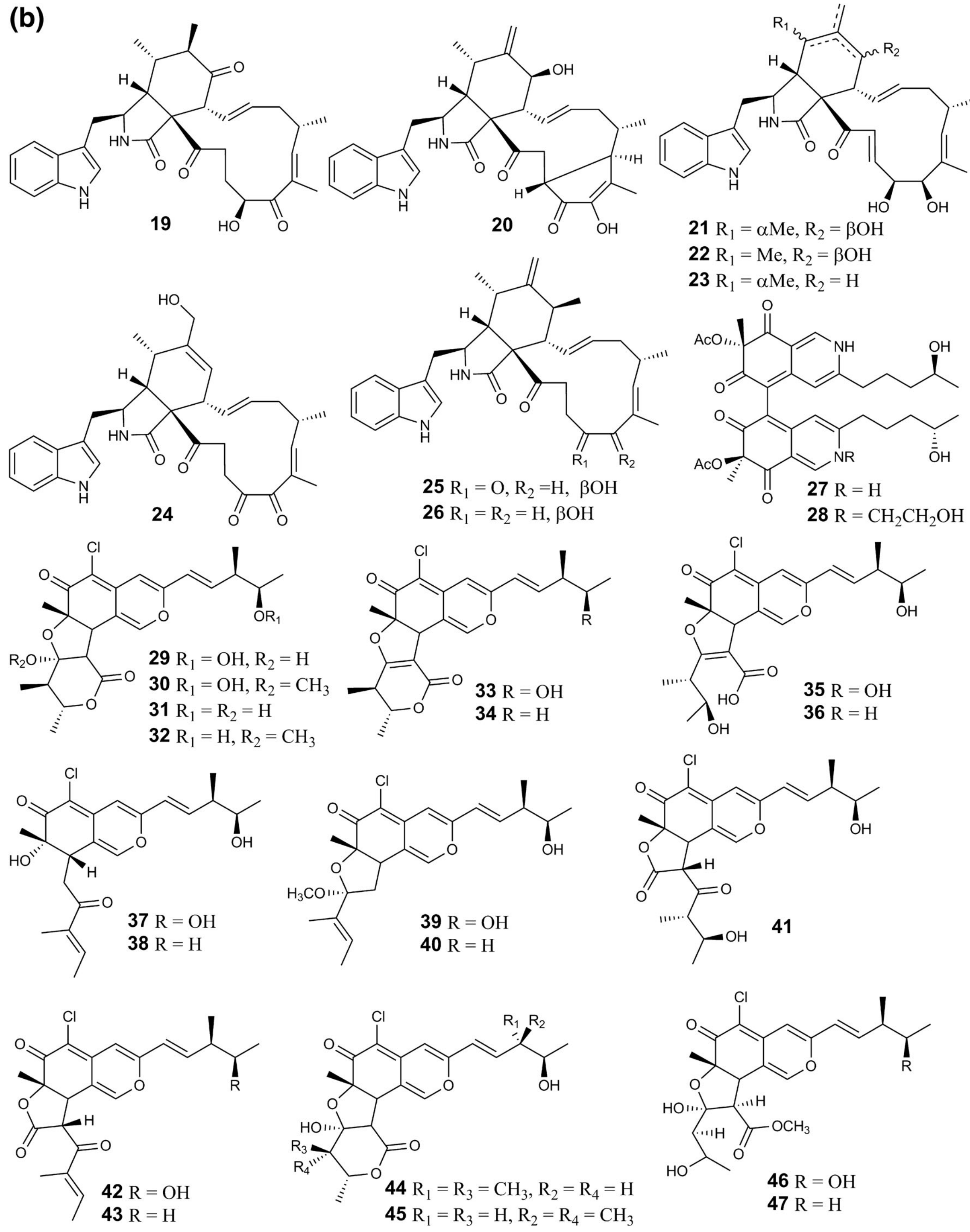

Fig. 1 continued

globosum, an endophyte of *M. cephalus*. These compounds significantly inhibited the growth of cultured P388, HL-60, L1210 and KB cell lines (Yamada et al. 2011) (Fig. 1c). Endophytic fungus separated from *G. biloba* led to isolation of three novel azaphilone alkaloids, chaetomugilides A–C (**52–54**) along with related compounds (**55–57**) from methanol extract of *C. globosum* TY1 (Fig. 1c). These compounds showed significant cytotoxic effects against cancer cell line HepG2 with the IC_{50} values ranging from 1.7 to 53.4 μM (Li et al. 2013).

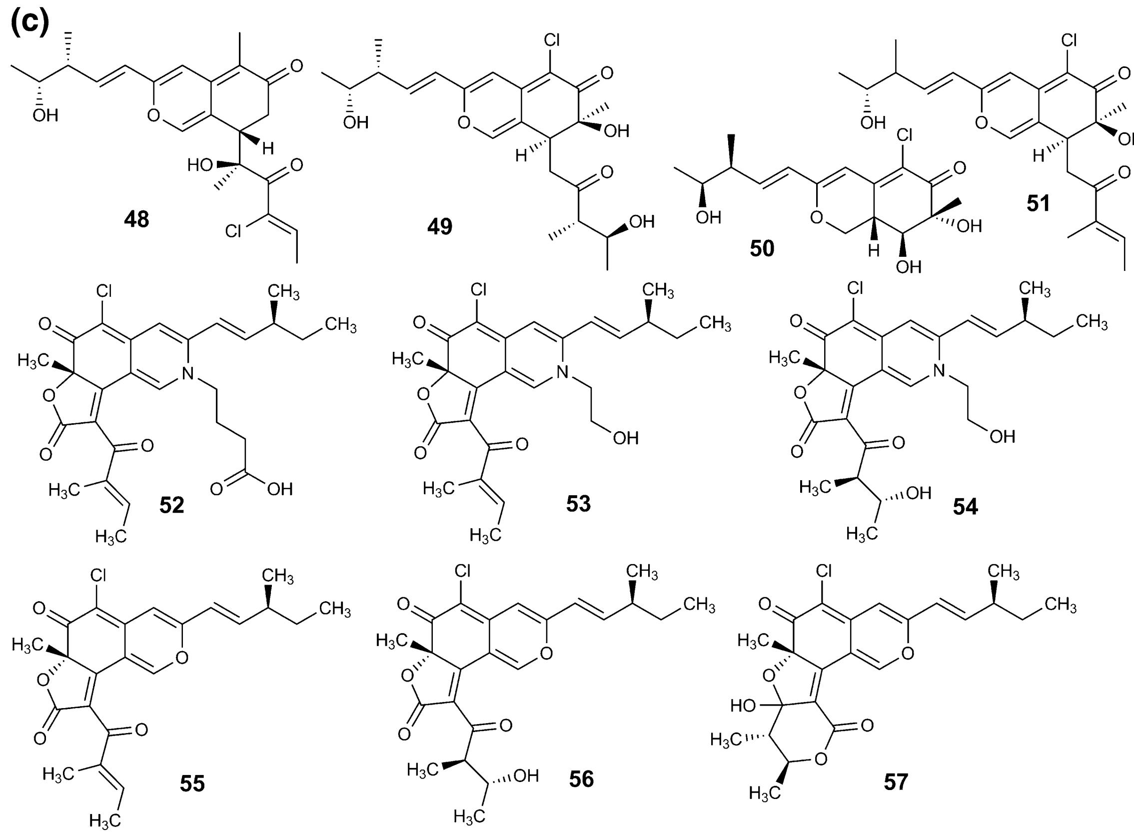

Fig. 1 continued

Other classes of cytotoxic metabolites

Chaetominine (**58**) is a cytotoxic tripeptidal alkaloid, isolated from *Chaetomium* species IFB-E015, an endophytic fungus of *A. axilliflora.* The compound showed cytotoxic activity against the human leukemic cell line K562 and colon cancer cell line SW1116 with IC_{50} values of 21 and 28 nM, respectively (Jiao et al. 2006).

A cytotoxic compound oosporein (**59**) was isolated from endophytic *C. cupreum* associated with *Macleaya cordata*. Oosporein showed antitumor activities against HL60 and A549 with IC_{50} values ranging 27–28 μM (Mao et al. 2010). Three new Orsellides (globosumones A–C) and known compounds (**60–64**) were isolated from *C. globosum*, an endophyte of *E. fasciculate* (Fig. 1d). These compounds were studied for cytotoxic activity against four cancer cell lines, MIA Pa Ca-2 (pancreatic carcinoma), NCI-H460 (non-small cell lung cancer), SF-268 (central nervous system glioma) and MCF-7 (breast cancer) and normal human fibroblast cells (WI-38). Only globosumones A (**60**) and B (**61**) were moderately active (Bharat et al. 2005).

A novel polyhydroxylated C29-sterol globosterol (**65**) and three known derivatives, 9-hydroxy cerevisterol (**66**), 9(11)-dehyoergosterol peroxide (**67**) and ergosta-4,6,8,22-tetraen-3-one (**68**) have been purified from *C. globosum* ZY-22, an endophyte of *G. biloba* (Qin et al. 2009b). Compound **66** exhibited striking cytotoxic activity against the HeLa cells (human cervical cancer cells) (Koyama et al. 2002). Ergosterolperoxide and 9(11)-dehydroergosterol peroxide (**67**) suppress the growth of mouse lymphocytes (Fujimoto et al. 1994). Sterol compounds were also reported from *C. globosum* L18, an endophyte of *C. wenyujin* (Wang et al. 2012).

Two novel polyketides, chaetochromones A and B (**69**, **70**) were purified from the crude extract of *C. indicum* endophytic fungus (CBS.860.68) together with three known compounds PI-3, PI-4 and SB236050 (**71–73**). These compounds showed minor inhibitory cytotoxic activities against A549 (adenocarcinomic human alveolar basal epithelial cells), PANC-1(human pancreatic carcinoma) and MDA-MB-231(breast adenocarcinoma) cancer cell lines (Lu et al. 2013) (Fig. 1d). A new depsidone namely chaetosidone A (**74**) together with six known fungal metabolites corynesidone B (**75**), corynether (**76**), kojic acid (**77**), ergosterol, ergosterol peroxide and adenosine were obtained from *Chaetomium* sp., an endophytic fungus isolated from *Zanthoxylum leprieurii* leaves. Chaetosidone A (**74**), corynesidone B (**75**) and corynether (**76**) displayed moderate toxicity towards brine shrimp larvae (*Artemia salina*) (Talontsi et al. 2013).

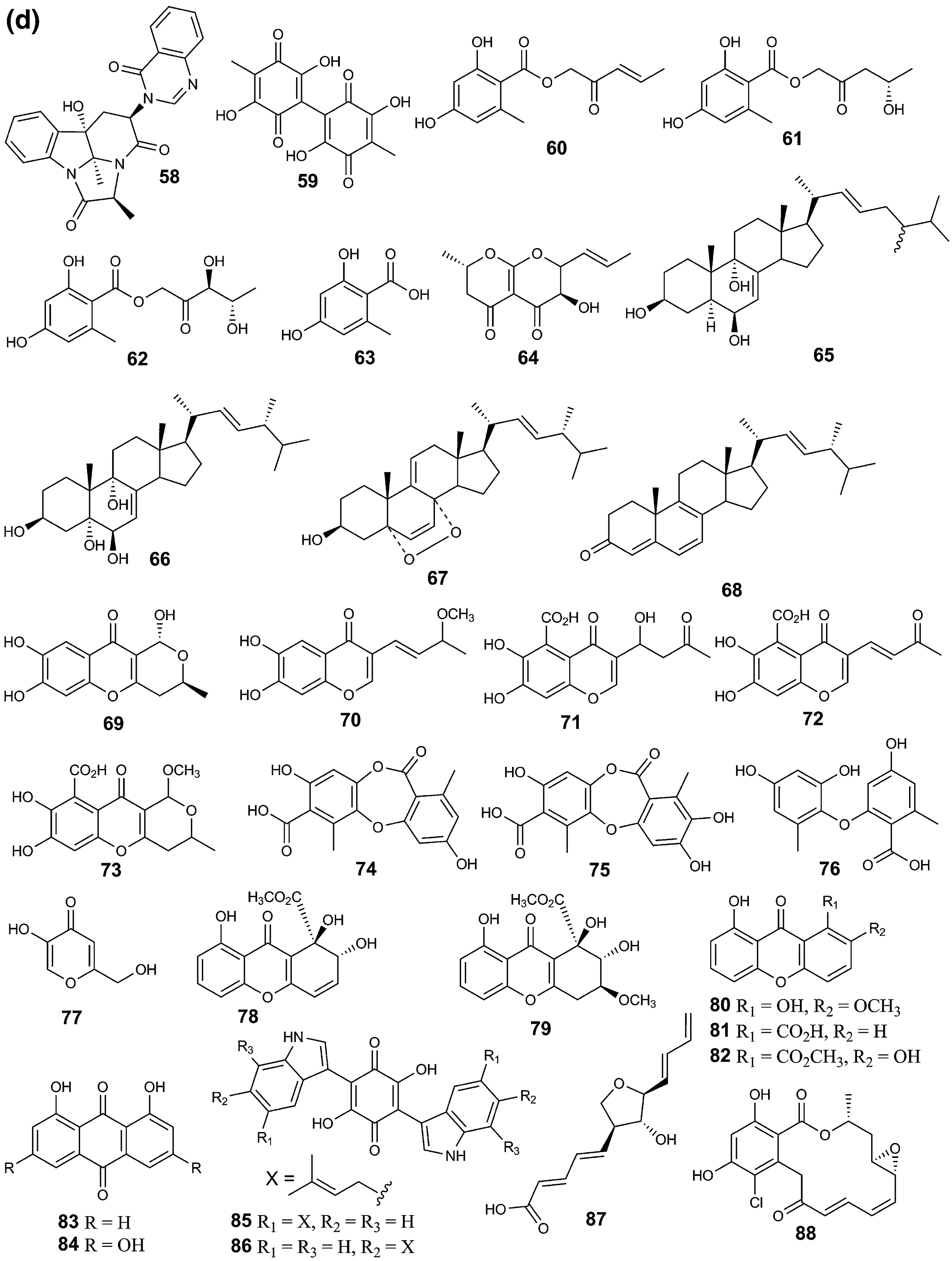

Fig. 1 continued

Five new xanthone derivatives, globosuxanthones A–D (**78–81**), 2-hydroxyvertixanthone (**82**), two known anthraquinones chrysazin (**83**) and 1,3,6,8-tetrahydroxy anthraquinone (**84**), have been isolated from extracts of the *C. globosum*, an endophyte of *Opuntia leptocaulis* DC (*Cactaceae*). Globosuxanthone A (**78**) showed potent cytotoxicity against seven cancer cell lines LNCaP (androgen-sensitive human prostate cancer), NCIH460 (Human lung

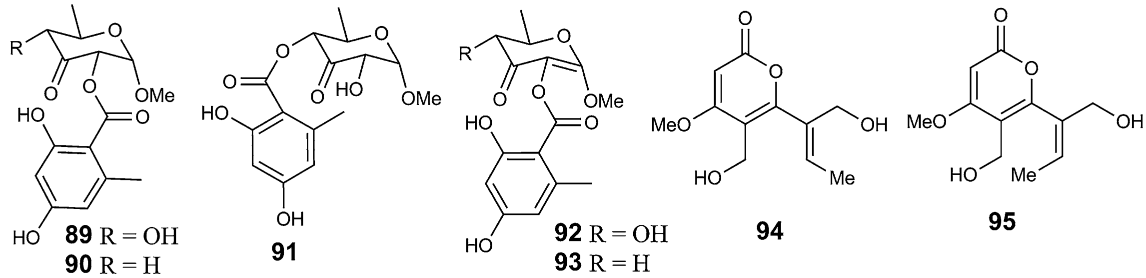

Fig. 2 Antibacterial metabolites from *Chaetomium* endophyte (**89–95**)

cancer), SF-268 (glioblastoma cell lines), PC-3 (human prostate cancer) and MCF-7 with IC_{50} values ranging from 0.65 to 3.6 µM (Wijeratne et al. 2006). Two cytotoxic metabolites cochliodinol (**85**) and isocochliodinol (**86**) were isolated from *Chaetomium* sp., endophytic fungus of *S. officinalis* (Debbab et al. 2009). Cochliodinol and isocochliodinol showed EC_{50} of 7.0 and 71.5 µg ml^{-1}, respectively, when tested for cytotoxicity against L5178Y mouse lymphoma cell (Fig. 1d).

A new tetrahydrofuran derivative, aureonitolic acid (**87**) along with known cochliodinol (**85**), isocochliodinol (**86**) and orsellinic acid (**63**), was reported from *Chaetomium* sp., an endophyte of *O. maritimus.* Compounds **85** and **63** showed significant growth inhibition with EC_{50} values of 7.0 and 2.7 µg ml^{-1}, respectively, when tested against L5178Ymouse lymphoma cells (Aly et al. 2009). Radicicol (**88**), a heat shock protein 90 (Hsp90) inhibitor, was purified from the extract of *C. chiversii* associated with Sonoran desert plant (Turbyville et al. 2006). Radicicol was reported as an anticancer compound (Na et al. 2001) (Fig. 1d).

Extracts studied for cytotoxic activities

Lu et al. studied the cytotoxic effects of extract produced from endophytic *C. globossum* against brine shrimp larvae which showed IC_{50} value of 7.71 µM ml^{-1} (Lu et al. 2009). Ether extract of *C. fusiforme* also exhibited cytotoxic activity against HL-60 and A549 cell lines with IC_{50} values below 50 µg ml^{-1} (Guo et al. 2008). Extract of *C. globossum* isolated from *Gloriosa superba* showed significant cytotoxic effects (Budhiraja et al. 2012). In another study, ethyl acetate extract of *Chaetomium* species isolated from *S. verrucosa* showed moderate cytotoxic effect in brine shrimp assay (Wu et al. 2013). Selim et al. also reported that ethyl acetate extract of *C. globossum* endophyte of *A. capillus* showed significant cytotoxicity of 55 % toward HepG-2 cells at 100 µg ml^{-1} and 66 % towards FGC_4 (fast growing colony) cells at 250 µg ml^{-1} (Selim et al. 2014).

Antimicrobial metabolites

Endophytes containing antimicrobial potential have been isolated from plants of various regions of the world. Endophytes have the ability of resistance mechanism to overcome pathogen invasion due to the production of secondary metabolites (Tan and Zou 2001). Exploring a novel or new antimicrobial metabolite is a significant substitute to overcome drug resistance. In various studies, scientists have reported antimicrobial potential of extracts and compounds isolated from endophytic *Chaetomium* species.

Antibacterial

The antibacterial orsellides A–E (**89–93**) were isolated from *Chaetomium* species (strain Go 100/9), an endophyte marine algae (Schlörke and Zeeck 2006). Extracts of *Chaetomium NoS3* were found active against bacterial strains *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus*, *Salmonella anatum* and *Escherichia coli* with minimum inhibitory concentration (MIC) ranging between 1 and 10 mg ml^{-1} (Huang et al. 2007b). Chaetoglobosin B (**2**) exhibited weak antibacterial activity against *E. coli* (MIC 189 µg ml^{-1}) and *S. aureus* (MIC 120 µg ml^{-1}) (Momesso et al. 2008). Ethyl acetate and dichloromethane extracts of *Chaetomium* species isolated from leaves of *A. indica* showed antibacterial activity against *Bacillus subtilis*, *Klebsiella pneumonia* and *S. aureus* (Gangadevi et al. 2008). Chaetoglocins A (**94**) and B (**95**) were new pyranones purified from *C. globosum* IFB-E036, an endophytic fungus (Fig. 2). Significant antimicrobial activity of these compounds against the Gram-positive bacteria was observed with MIC values ranging between 8 and 32 µg ml^{-1} (Ge et al. 2011). Chaetosidone A (**74**), corynesidone B (**75**) and corynether (**76**) displayed inhibitory effects on two Gram-positive bacteria, *S. aureus* and *B. subtilis* at concentrations of 40 µg per disc (Talontsi et al. 2013) (Fig. 2). In another study, significant antibacterial activity of ethyl acetate fraction of *Chaetomium* endophytes of *S. verrucosa* was

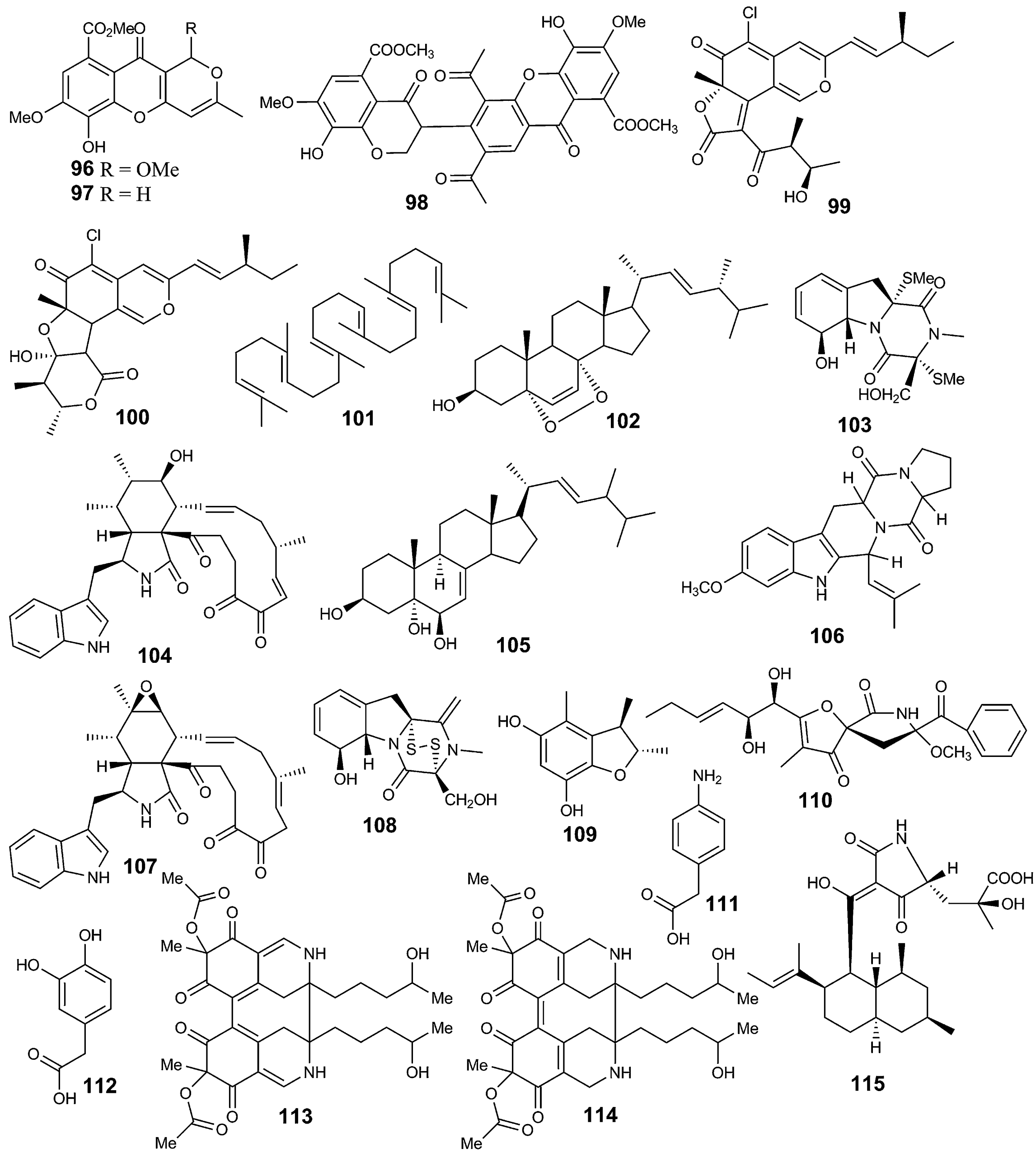

Fig. 3 Antifungal compounds from *Chaetomium* endophyte (**96–115**)

observed against methicillin-resistant *S. aureus* (MRSA) (Wu et al. 2013).

Antifungal metabolites

Chaetocyclinones A–C (**96–98**), the three new metabolites were produced by *Chaetomium* sp., Gö 100/2, an endophyte from marine algae. Compound **96** exhibited fungistatic activity against a phytopathogenic fungus, *Phytophthora infestans* (Zhang et al. 2012). The *C. globosum* F0142 produced two main metabolites, chaetoviridins A (**99**) and B (**100**) which exhibited antifungal activity (Fig. 3). Compound **99** exhibited higher antifungal activities against *Magnaporthe grisea* and inhibited emergence of rice blast disease 80 % at 62.5 µg ml^{-1} (Park et al. 2005). Ether extract of *C. fusiforme* showed significant antifungal potential against *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton rubrum*, *Aspergillus fumigates* and *Pycricularia oryzae* (Guo et al. 2008).

Qin et al. (2009a) also reported antifungal activities of metabolites of *C. globossum*, an endophyte of *G. biloba*.

Extract of *C. globossum* showed more than 60 % inhibition against *Rhizoctonia solani*, *Nigrospora oryzae*, *Macrophomina phaseolina*, *Phoma sorghina* and *Alternaria alternata* (Naik et al. 2009). Ethyl acetate extract of *Chaetomium* species isolated from *Taxus baccata* also showed antifungal activity (Tayung and Jha 2010). Oosporein (**59**) isolated from endophytic *Chaetomium* sp. showed significant antifungal activity against *R. solani*, *Botrytis cinerea* and *Pytium ultimum* (Mao et al. 2010). Metabolites (**101–112**) of *C. globosum* originated from *G. biloba* were tested for antifungal potential (Li et al. 2011) (Fig. 3). Compound **108** (gliotoxin) showed good antifungal activity against *Fusarium sulphureum*, *A. alternata* and *Claviceps sorghi* with EC_{50} values of 68.5, 36.8 and 59.8 μg ml^{-1}, respectively (Li et al. 2011).

In 2011, Kumar et al. (2011) reported that the extract of *Chaetomium* sp. exhibited mild antifungal activity against *Fusarium oxysporum* and *Sclerotinia sclerotiorum*. Ethyl acetate and dichloromethane extracts of endophytic fungus *C. atrobrunneum* showed antifungal activity (Srimathi et al. 2011). Cheatoglobosin X (**16**) isolated from endophytic fungus *C. globossum* L18 exhibited antifungal activity against *Exserohilum turcicum*, *F. oxysporum* and *Curvularia lunata* with an MIC value of 3.125 μg ml^{-1} (Wang et al. 2012). New azaphilone alkaloids, cheatofusins A (**113**) and B (**114**) from endophytic *C. fusiforme* were also tested for antifungal activity (Peng et al. 2012). Compounds exhibited powerful antifungal activity against the fungus *C. albicans* ATCC76615 (IC_{50} 8 and 4 μg ml^{-1}, respectively) and *Aspergillus fumigatus* (IC_{50} 4 and 4 μg ml^{-1}, respectively). In another study, chloroformic and butanolic extract obtained from endophytic *C. globossum* showed antimicrobial potential (Budhiraja et al. 2012). Kumar and his colleagues reported antifungal activity of an antibiotic Sch 21097 (**115**) isolated from ethyl acetate fraction of *C. globossum* L18 (Kumar et al. 2013**)** (Fig. 3). Extracts of *C. globossum* No.04, an endophyte of *G. biloba*, showed antifungal effect against *Coniothyrium diplodiella* and *Rhizopus stolonifer*. Further chemical investigation of *C. globossum* No.04 led to purification of chaetoglobosin A (**1**) C (**3**), D (**4**), E (**5**), G (**12**) and R (**17**) metabolites. These compounds showed remarkable antifungal activity against *Coniella diplodiella* with % inhibition ranging from 54.73 to 73.07 % at a concentration of 20 μg per disc (Zhang et al. 2013a, b).

Miscellaneous antimicrobial metabolites

Chaetoglobosin B (**2**) was isolated from *C. globossum* endophyte, an endophyte of *M. hookeri* which showed activity against *Mycobacterium tuberculosis,* a causative agent of tuberculosis (Ni et al. 2008). Cerebrosides C (**116**), B (**117**) and allantoin (**118**) were purified from an endophyte *C. globosum* ZY-22. Cerebroside C (**116**) has elicitor activity in plants (Qin et al. 2009c). Borges et al. (2011) reported isolation of thirteen chaetoviridines (**119–131**). Six known chaetoviridins A–E (**119–123**), 4′-epichaetoviridin A (**125**), six new 5′-epichaetoviridin A (**124**), 4′-epichaetoviridin F (**126**), 12β-hydroxychaetoviridin C (**127**) and chaetoviridins G–I (**128–130**) were purified from the endophytic fungus *C. globossum* (Fig. 4). The antibiotic activities of the compounds were evaluated using in vivo *Caenorhabditis elegans* infection model (Borges et al. 2011).

Enzyme inhibitors

Enzymes are considered to be the striking targets to treat human diseases by intervention of small drug molecules. Enzymes play a critical catalytic role in many physiological processes altered in the diseased conditions (Schomburg et al. 2013). The study of enzymes is to identify inhibitory molecules considered a key step for drug discovery. Therefore, the study of natural metabolites as enzyme inhibitors is an active area of research in biochemistry and pharmacology.

Three novel chemokine receptor inhibitors, Sch 210971 (**131**), Sch 210972 (**132**) and Sch 213766 (**133**), were isolated from *C. globosum*, an endophyte of plants of Arizona (Yang et al. 2006, 2007). These compounds showed significant inhibitory activities with IC_{50} values of 1.2, 0.079 and 8.6 μM, respectively. Chemokine receptor CCR-5 inhibitors have potential therapeutic applications in the treatment of human immunodeficiency viral (HIV) infections.

A marine *Chaetomium* sp. produced a novel benzonaphthyridinedione derivative, chaetominedione (**134**) (Fig. 5). Chaetominedione showed significant p56lck tyrosine kinase inhibition of 93.6 % at 200 μg ml^{-1} (Abdel-Lateff 2008). Tyrosine kinase enzymes are involved in many immunological functions in human body. Ethyl acetate extract of *C. globossum* JN711454 showed 85 % inhibition of butyrylcholinestrase enzyme (Selim et al. 2014). Butyrylcholinesterase are hydrolytic enzymes that act on acetylcholine. Butyrylcholinesterase activity progressively increases in patients with Alzheimer's disease. Therefore, inhibition of this enzyme is important therapeutically (Zhao et al. 2013).

Antimalarial and antitrypanosomal activity

Malaria and trypanosoma are parasitic protozoans. Infections caused by these organisms are contagious. Current treatments act on a limited number of targets (Vial et al. 2013). Therefore, the next challenge is to identify new classes of drugs that will attack novel molecular targets

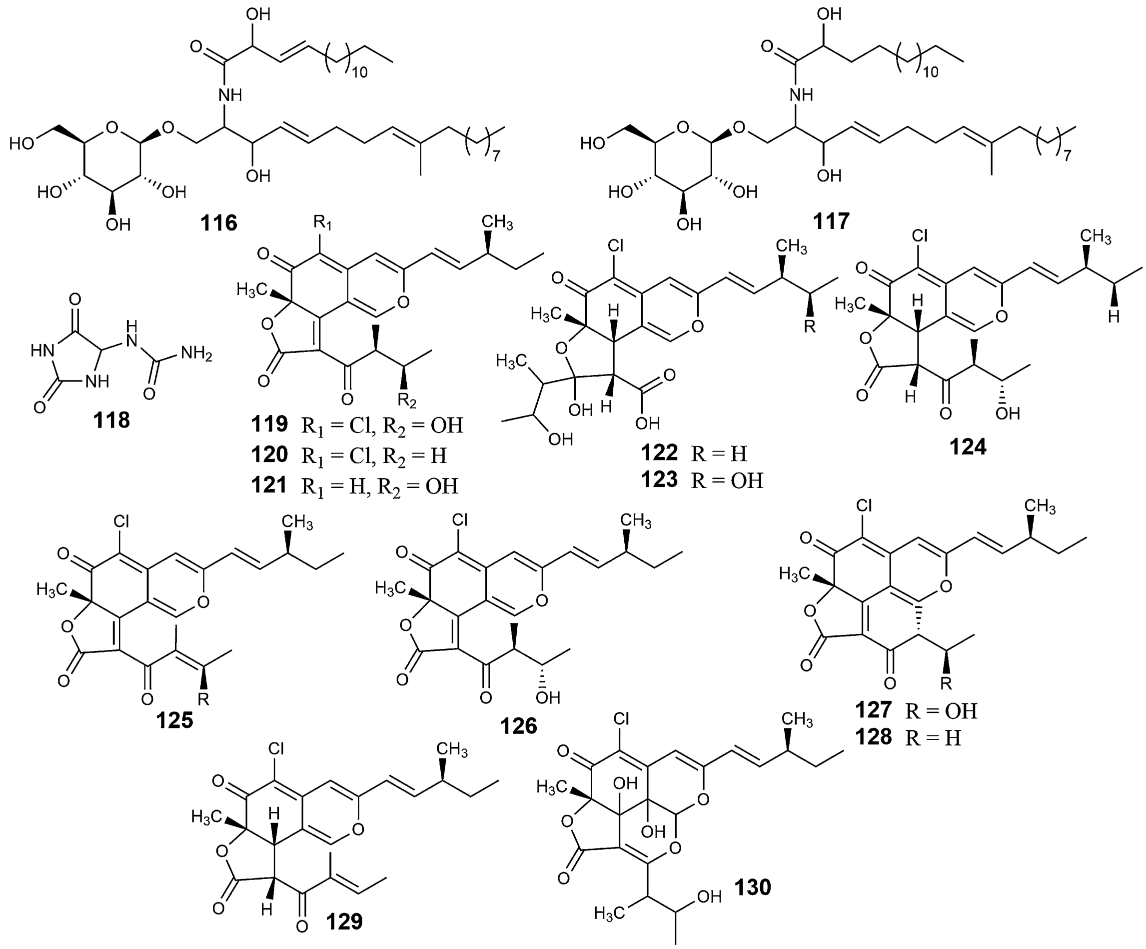

Fig. 4 Miscellaneous antimicrobial metabolites from *Chaetomium* endophytes (**116–130**)

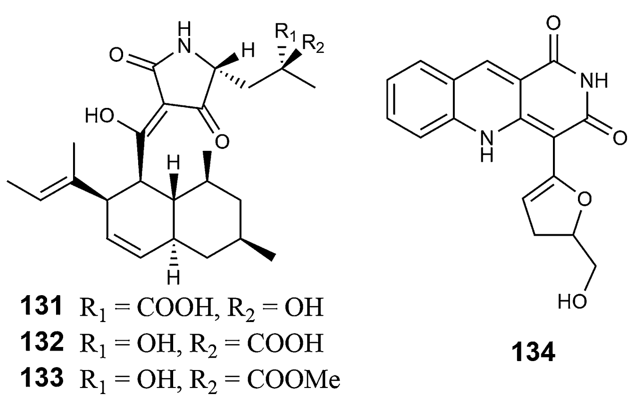

Fig. 5 Enzyme inhibitors from *Chaetomium* endophytes (**132–134**)

with sufficient therapeutic efficacy to combat rapid development of resistance (Cowman et al. 2000). Pontius et al. (2008) studied antiparasitic potential of marine *Chaetomium* fungus and reported isolation and purification of three new chaetoxanthones A–C (**135–137**) (Pontius et al. 2008). Compound **136** showed selective activity against *Plasmodium falciparum* with IC_{50} value of 0.5 µg ml^{-1} while **137** was moderately active against *Trypanosoma cruzi* (Fig. 6).

Antioxidant metabolites

Human cells when exposed to oxidative species undergo various genetic modifications due to free radicals (Dizdaroglu et al. 2002). These modifications can initiate carcinogenesis (Valko et al. 2004). To protect the cells from this damage, it is necessary to search for new free radicals scavengers from the natural sources. Most of the plants and microorganisms have been investigated for their antioxidant potential (Haq et al. 2012; Ravindran et al. 2012). Cultivation of *C. globosum,* an endophyte of red alga, leads to the isolation of a new benzaldehyde derivative chaetopyranin (**138**) along with three known metabolites (**139–141**) benzaldehyde congeners, 2-(2′,3-epoxy-1′,3′-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl) benzaldehyde (**139**), isotetrahydroauroglaucin (**140**) and erythroglaucin (**141**). These compounds showed moderate antioxidant activity (Wang et al. 2006). *Chaetomium* sp. isolated from *N.*

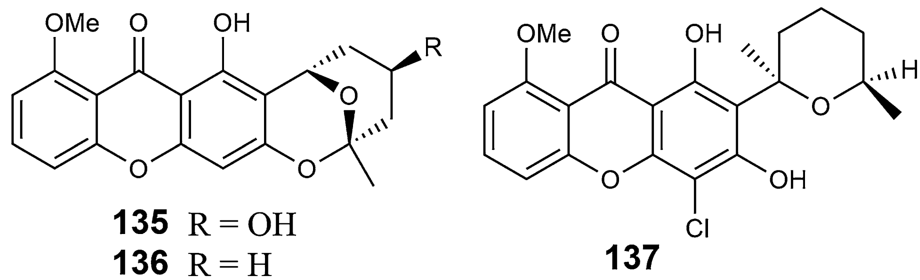

Fig. 6 Antimalarial metabolites from *Chaetomium* endophytes (**136–137**)

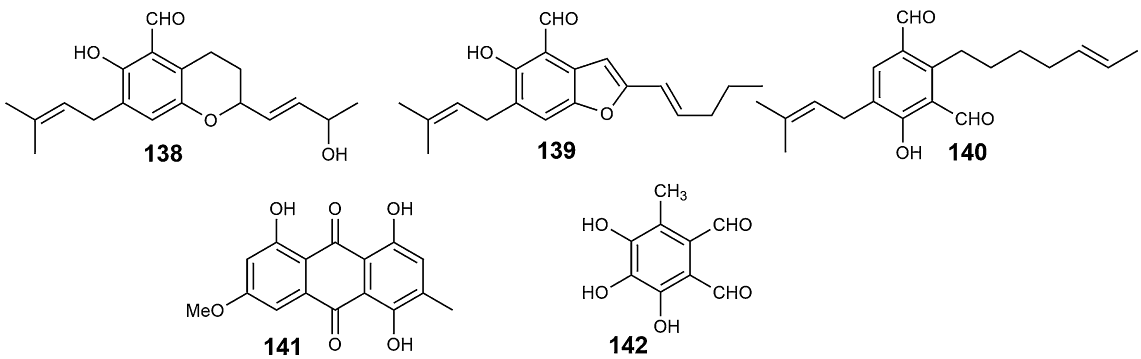

Fig. 7 Antioxidant metabolites from *Chaetomium* endophytes (**139–142**)

oleander showed potent antioxidant activity because of the presence of phenolic and flavonoids (Huang et al. 2007a). Another antioxidant compound flavipin (**142**) showing IC_{50} value of 6.3 μg ml^{-1} in an antioxidant assay was also isolated from endophytic *C. globosum* CDW7 (Ye et al. 2013) (Fig. 7). Ethyl acetate extract of *C. globosum* JN711454 showed antioxidant activity with IC_{50} value of 11.5 μg ml^{-1} (Selim et al. 2014). Extract of endophytic *Chaetomium* sp. of *Eugenia jambolana* also showed 80 % antioxidant activity (Yadav et al. 2014).

Conclusion

Based on the studies, it can be concluded that endophytic fungi hold a lot of therapeutic potential. Current review depicts that *Chaetomium* endophytes producing chemically and pharmacologically diverse secondary metabolites can be a potential source of drug lead molecules for future studies.

Author contribution statement All authors contributed equally for revisions and development of manuscript.

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