Bioprospecting and biodiversity investigations of endophytic fungi isolated from medicinal plants and mosses

Ph.D. dissertation

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2020

Szeged

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2 List of abbreviations

BGC	Biosynthetic Gene Cluster
BLAST	Basic local alignment search tool
CDB	Czapek dox Broth
CR	Colonization Rate
DAD	Diode Array Detector
DM	Defined Medium
EF	Endophytic fungi
EtOAc	Ethyl acetate
HPLC	High Performance Liquid Chromatography
IR	Isolation Rate
ITS	Internal transcribed spacer
MALDI	Matrix-assisted laser desorption/ionization
MeCN	Acetonitrile
MEB	Malt Extract Broth
MeOH	Methanol
MS	Mass Spectrometer
NB	Nutrient Broth
NCBI	National Center for Biotechnology
PCR	Polymerase chain reaction
PDA	Potato Dextrose Agar
PDB	Potato Dextrose Broth
PKS	Poly ketide Synthase
RA	Relative abundance
SZMC	Szeged Microbiological Collection

3 INTRODUCTION

3.1 Significance of natural products

Throughout evolution, the dependence of human beings on nature has been everlasting. Natural products have been one of the important sources of medicine for millennium to alleviate and treat various diseases. The increasing prevalence of new diseases results in the continuous need of exploiting natural products for drugs (Li et al. 2019). Especially, the emergence of multidrug-resistant microbes increases the urge to find novel therapeutic lead (Spera et al. 2019). Despite the rise of combinatorial chemistry as an integral part of lead discovery process, natural products still play a major role in providing novel and interesting chemical scaffolds for drug discovery with an outstanding development in the areas of separation science (Liu et al. 2019). The comprehensive review by Newmann and Cragg (2016), provides detailed information about the natural compounds discovered in between 1981-2014. Out of 1562 new chemical entities (NCE) discovered in this period, 73% belongs to natural products and their derivatives and only 27% of the drugs were of synthetic origin. The technological advancement in omics enhances the domineering contributions of natural products in drug discovery (Newman and Cragg, 2016).

Natural products include either a complete organism like a microbe, a plant or an animal or part of an organism or the extracts of an organism and in most cases the term natural products denotes to secondary metabolites, which are small molecules (MW < 2000 Da) produced by organisms that are not firmly needed for the existence of an organism. The secondary metabolites like terpenoids, coumarins, alkaloids, glycosides, flavonoids, steroids, sugars, lignans etc., are generally considered as medicinally important (Mushtaq et al. 2018). According to the analysis reported on Annual reports of Medicinal Chemistry, over 65% to 75% of drugs developed from 1983 to 1994 for infectious diseases and deadly diseases like cancer are derived from natural sources (Arnold, 2007).

Although plants are considered as the bio factories of many valuable bioactive compounds, they possess the disadvantage of slow growth rate and harvesting rare and endangered species also poses a risk (Jia et al. 2016). Therefore, it is necessary to find alternative approaches to produce medicinal plant derived bioactive metabolites. Discovery of penicillin in 1929 paved the way to

use microorganisms as a source of potential drug candidates (Gaynes, 2017). According to recent reports, only 5 % of the world's fungal and 0.1 % of bacterial species have been described yet and a small fraction of them has been explored for their bioactive compounds (Thomas et al. 2011). Recent research estimates that currently more than 1 million natural compounds have been isolated, from which 50-60 % have plant and 5 % have microbial origins (Demain and Sanchez, 2009). In recent decades, endophytes have been recognized as a source of several bioactive compounds and are studied as potential sources of novel natural products for medical and commercial exploitation (Selvakumar et al. 2018). The endophytic bioactive metabolites possess a wide variety of biological activities as their antimicrobial-, antitumor-, antioxidant-, anti-inflammatory, etc. activities have been previously identified (Selvakumar et al. 2018).

3.2 Endophytic fungi – The hidden world within plants

3.2.1 General characterization of endophytic fungi

Endophytic microbes are an intriguing group of microorganisms that play a vital role in enhancing plant growth and are also a well-known source of bioactive secondary metabolites (Sahoo et al. 2017). The term “endophyte” originally introduced by de Bary to distinguish fungi - living inside host tissues - from epiphytes, is derived from the Greek word “endon” meaning inside or within and “phyton” meaning plant (Bary, 1866). The meaning of the word has evolved to include any microorganism that inhabits plants during a period of its life cycle, especially within their leaves, branches, and stems, without causing significant damage to its host (Wilson, 1995). They are mainly fungi, which have been in co-evolution with their eukaryotic hosts for millions of years (Heckman et al. 2001). Endophytic fungi (EF) can also be defined as an ecological group of fungi colonizing the inner tissues of plants without any recognizable features of their presence. The ubiquity of EF has been revealed by many studies that estimate close to one million species residing in plants (Dreyfuss and Chapela, 1994) lichens (Li et al. 2007) and mosses (Zhang et al. 2013).

Endophytes possess a complex relationship with their hosts. They are symbiotic in nature, which may be mutualism, commensalism or saprophytism (Clay and Schardl, 2002; Strobel and Daisy, 2003). Although, almost all higher plants contain at least one endophytic microbe, the relationship between microbes and their plant hosts remains one of the least studied biochemical

systems, because it is difficult to find the exact physical relationship in the interaction (Strobel, 2003). It has been reported that these endophytes have co-evolved with the higher plants since their existence as they have been isolated from fossilized tissues of stems and leaves (Bacon and White, 2000). Given this fact, this long-held association might have created a specific genetic system in endophytes their relationship with plants or vice versa (Strobel, 2003). Furthermore, the independent evolution of the endophytes might also have devised them for better adaptation to their host and contributes to their biochemical pathway (Strobel, 2003).

Endophytes are considered to be evolved within distant phylogenetic groups of fungi similar to mycorrhizal fungi. According to Brundrett et al. (2006), EF are facultative plant symbionts. Unlike mycorrhizal fungi, their development does not synchronize with the development of their host and they can complete their life cycle outside the host organism (Brundrett et al. 2006). Another distinctive feature that differentiates endophytes from mycorrhizal fungi is that they can also inhabit host tissues above the ground level like stem, leaves and barks (Petrini, 1996).

3.2.2 Classification of fungal endophytes

According to Schaechter (2012), EF have been divided into two groups based on their taxonomical difference, host range, patterns of colonization and transmissions, ecological function and tissue specificity (Schaechter, 2012). The two groups are the clavicipitaceous and non-clavicipitaceous (NC) EF infecting grass and found in vascular and non-vascular plants, respectively.

Another classification is proposed by Rodriguez et al. (2009), in which EF are classified into four classes based on the phylogeny data and life history traits (Rodriguez et al. 2009). The class I includes symbiotic species associated with insects, fungi, grasses, and rushes (Bacon and White, 2000). They are mainly found in grass family Poaceae, rarely in Cyperaceae, and are often vertically transmitted through seeds that mostly belong to the Hypocreales order of the Ascomycota phylum. Most of the clavicipitaceous fungi belonging to this class colonize intracellular spaces of leaf sheaths, rhizomes, and leaf blades (White et al. 1996). They play a major role in insects and mammalian herbivore deterrence by producing alkoloidic compounds such as loline, peramine

(Clay, 1990) as well as ergot and lolitrem alkaloids (White and Bultmann, 1987; Gentile et al. 2005). Studies have also proved that EF of this class are active against nematodes as the infection of *Festuca arundinacea* with an endophytic fungus *Acremonium coenophialum* has been shown to reduce the nematode populations in agricultural field soils (Kimmons et al. 1990). Some clavicipitaceous endophytes from *Epichloe festucae* were found to be producing indole derivative compounds, sesquiterpene and diacetamide that can inhibit plant pathogenic fungi (Yue et al. 2000)

Rodriguez et al. (2009) proposed that NC endophytes represent three groups (class II, class III and class IV based on host colonization, transmission in biodiversity of plants and benefits conferred to hosts (Rodriguez et al. 2009). Class II EF colonize roots, shoots and leaves of monocotyledon and dicotyledon plants. They form a specific ecological group, which colonizes plants growing in stressful habitats and are highly diverse (Watkinson, 2016). Class III endophytes are distinct as they restrict their colonization to above-ground plant tissues, and their infection is localized mainly on leaves and twigs of host plants (Arnold, 2007). This group is also highly diverse and consists of mainly Pezizomycotina and Saccharomycotina (Ascomycota) species, as well as Agaricomycotina, Pucciniomycotina and Ustilagomycotina (Basidiomycota) species. They spread horizontally through spores and hyphal fragments (Arnold, 2007).

Class IV endophytes are found in the rhizosphere, which is another common habitat with high diversity. These endophytes are often misidentified as mycorrhizal fungi (Jumpponen, 2001; Rodriguez et al. 2009). The endophytes of this class have a broad host range, with over 600 known plant species as hosts (Jumpponen and Trappe, 1998).

3.2.3 Biodiversity of endophytic fungi

EF are highly diverse, and more than 1 million species of this fungal group is estimated to be undiscovered (Sun and Guo 2012). A survey conducted on fungi of various hosts in the past 20-30 years demonstrates that colonization of endophytes on land plants is ubiquitous (Petrini, 1996; Nisa et al. 2015). Extensive studies on species distribution, biological and ecological aspects of endophytes in Europe and North America have been conducted for years (Petrini, 1996;). Although endophytes have been identified from plants in various habitats in tropical, temperate and boreal forests (U'Ren et al. 2019), they are mostly confined to gymnosperms in temperate regions

(Bernstein and Carroll, 1977). EF have also been detected in grasses (Bacon et al. 1977) and hepatics (Stone et al. 2004). They are also found in non-vascular plants (Zhang et al. 2013), algae (Hawksworth, 2001), ferns, fern allies (Schulz et al. 1993; Fisher, 1996) and mosses (Zhang et al. 2013). Endophytic fungal diversity is high in tropical forests where the diversity of woody angiosperm is also high (Banerjee, 2011).

EF represent an important component of fungal biodiversity and it has also been observed that almost every plant examined to date harbors at least one species of EF and many plants, particularly woody plants, contain hundreds of endophytic species (Petrini, 1986; Sahoo et al. 2016). Remarkable efforts have been made to estimate the total number of fungi on the basis of their association with plants (Hawksworth, 2001). The magnitude of fungal diversity was estimated to be around 1.5 million species (primarily based on a ratio of vascular plants to fungal species of 1:6) that has been later revised to 2.27 million (Hawksworth, 2001). Dreyfuss and Chapela (1994) estimated that EF of the 270,000 plant species that exist on this planet could be colonized by 1.38 $\times$ 10^6 unique fungal species. However, the number of fungal species may vary because of the availability of modern tools and techniques of identification.

It has been reported that EF belong to diverse phyla, which includes Ascomycota, Basidiomycota and Mucormycota groups. Various factors affect the distribution of the EF community such as environmental factors (temperature, humidity), and the type and age of the colonized host tissue (Sanchez-Azofeifa et al. 2012). Several studies showed that distribution of EF is higher in older tissues than in younger tissues (Sanchez-Azofeifa et al. 2012). Most of the studies reported that Dothideomycetes and Soradariomycetes are the dominant classes found in medicinal plants, but the EF diversity also differs according to the geographical regions. A study carried out by Kharwar et al. showed that most of the EF isolated from *Catharanthus roseus* belonged to Hyphomycetes (Kharwar et al. 2008), whereas Dhayanithy et al. reported Dothideomycetes as the dominant class of the EF of *C. roseus* from coastal regions (Dhayanithy et al. 2019).

In the past two decades, the distribution and biodiversity of EF have been examined in different host plants. The most abundant EF species are *Alternaria, Aspergillus, Fusarium, Cladosporium, Penicillium, Trichoderma, Acremonium, Chaetomium, Neurospora, Epicoccum,*

Curvularia, Arthrinium (Rana K.L. et al. 2019). Still the number of undiscovered EF must be higher, as most of the studies followed traditional culture dependent methods to report EF diversity. By employing high throughput sequencing, more EF can be recovered, and EF diversity can be well documented (Sengupta et al. 2017).

3.2.4 Multifaceted interactions between endophytic fungi and the plants

Endophytes maintain a dynamic relationship with host plants. They can be symbionts, commensals, decomposers or latent pathogens (Promputha et al. 2007). They spend at least a part of their lifecycle inside the plant and are mutualistic with the host by increasing its defence mechanisms (Schulz et al. 1999). EF usually display a latent state inside their host for the whole lifetime of their host or for an extended period. Whenever the environmental conditions become appropriate for the fungus or when the ontogenetic state of the host turns to the benefit of the fungus, they might become pathogens (Strobel, 2016). Still the precise external or endogenous factors responsible for fungal transition from endophyte to pathogen are unknown. Therefore, to get better insights into the dynamics of endophytism, comparative studies on gene expressions needed to be carried out under conditions, where the same microbe behaves as a mutualist or a pathogen (Strobel, 2016).

Endophytes also increase the competitive abilities and fitness of plants by increasing their nutrient uptake, resistance to drought and water stress, tolerance to heavy metal stress and high salinity, or increasing growth rate through biochemical pathways by producing plant growth hormones. For example, researchers proved that most of the EF produce indole-3-acetic acid (Tan and Zou, 2001). It is also suggested that these endophytes also initiate the biological degradation of the dead or dying host tissues (Tan and Zou, 2001)

Endophytes are potential biocontrol agents as the ecological niche of their colonization is similar to that of phytopathogens. Interaction studies between grass and endophytes suggest that they are herbivore antagonists and enhance the growth of the plant (Clay, 1990). The literature also suggests that a large number of EF exhibit multiple ecological roles, as the endophytic fungus *Chaetomium globosum* plays a role of saprotrophs and pathogens (Arnold and Engelbrecht, 2007).

Lateral gene transfer phenomenon (LGT), which is important for colonizing the endosphere

region of plants plays a key role in promoting genetic and biochemical diversity **(**Tisserant et al. 2013; Arora et al. 2018). Researchers have reported that the number of bioactive natural products isolated from endophytes of tropical regions are higher compared to that of endophytes found in temperate regions and the metabolism is distinct (Banerjee, 2011). This suggests the significant role of the host plant in influencing the general metabolism of endophytic microbes. The presence of the putative terpene cyclases in the paclitaxel-producing endophytic *Penicillium aurantiogriseum* from hazel and comparison with 13 known paclitaxel biosynthetic genes from *Taxus spp*. showed high homology (Yang et al. 2014) is one of the remarkable examples showing a beneficial role of lateral gene transfer

There are limited studies related to LGT between endophytes and plants. Today it is possible to understand LGT events due to the progression of high-throughput genome analysis methods, thus more studies could be carried out to explore genetic recombination events and to examine the transfer of metabolic pathway genes between host plants and endophytes. The LGT is a key phenomenon that confers novel traits in eukaryotes and prokaryotes.

The background of host-endophyte interactions is an exciting field that is yet poorly investigated. It is uncertain that endophytes are either systemic or host specific and what they produce in culture and in nature. Although a range of factors affecting the host might also affect the endophytes, more information about physiological interaction with the host would be exceedingly helpful to understand their ecology. Between EF, endophytic bacteria have intensive cross-talks with associated hosts under the effect of various biotic factors like feeders and insects (**Figure 1**). During this interaction the endophytes could either live in a beneficial association with the host or turn into a pathogen lifestyle (**Figure 1**).

Furthermore, the cost-benefit interaction of plant-fungus could lead to either a mutual benefit/harm or relative benefit/harm (Figure 1D). This complex interaction can be represented as mutualism and ardent parasitism or exploitation (Kusari et al. 2014).

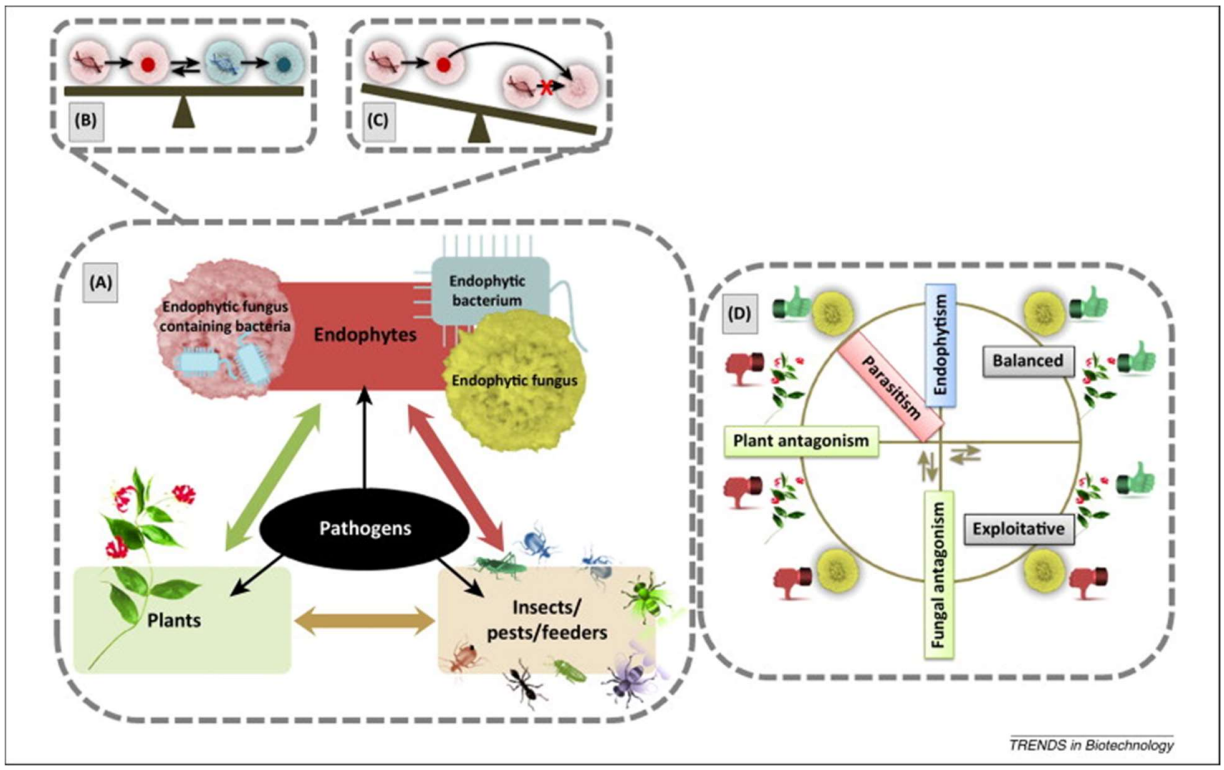

Figure 1. The complex interaction of plant-endophyte interface (Kusari et al. 2014). (A) Biological network and crosstalk connecting EF (B) Fair trade partnership between EF and other microbes (C) Cheater life style of EF (D) Plant–EF cost–benefit interactions mutual benefit (double thumbs-up) of both partners, relative benefit (single thumbs-up), relative harm (single thumbs-down) to one partner at the cost of the other, or harm to both interacting partners (double thumbs-down).

3.3 Significance of plant selection for bioprospecting endophytic fungi

EF of medicinal plants are potential sources of novel bioactive compounds and some have also been proved to be producing plant associated therapeutic metabolites (Huang et al. 2007). Moreover, the production of medicinally important phytochemicals from microbial sources is highly economical and easier, which increases the availability of products at reduced market price (Strobel, 2003). Due to the substantial number of plant species in the world, inventive strategies should be used to narrow the search and maximize the possibility of discovering endophytes producing novel bioactive compounds (Mittermeier et al. 2004)

A specific rationale can be utilized in governing the strategy of plant selection as follows:

(a) Plants from unique environmental settings, which possess an unusual survival strategy. In one study, the significance of endophytes isolated from an aquatic plant *Rhyncholacis penicillata* - collected from a river system in southwest Venezuela - has been investigated. It has been postulated that the aquatic environment created many portals, through which common phytopathogenic oomycetes could enter the plant tissues. However, the plant population appeared to be healthy, possibly due to protection from an endophytic product (Strobel, 2003).

(b) Plants that have been used by indigenous people with an ethnobotanical history could have interesting biological activities. It was found that the endophytes isolated from these plants possess higher antimicrobial activity than endophytes isolated from crops and plants in special environments (Strobel, 2018). It is reasonable to assume that the healing processes, might be facilitated by compounds produced by one or more plant-associated endophytes as well as the plant products themselves. Using this rationale, the plants of *Juniperus* was selected by Kusari et al. which has been used as a folk medicine. It contains therapeutically important anticancer compounds lignans, podophyllotoxin and deoxypodophyllotoxin. These compounds were also identified in the endophytic fungus *Aspergillus fumigatus* of *J. communis* (Kusari et al. 2009a).

(c) Plants that are endemic, endangered, have an unusual longevity, or that have occupied a certain ancient land mass, are also more likely to harbour endophytes with active natural products than other plants. Due to the medicinal value and economical importance of *Campotheca acuminate*, it has been harvested by various sectors around the world to isolate camptothecin (Lorence and Nessler, 2004; Sankar-Thomas, 2010). It has been proven that EF isolated from these plants also produced this compound and they may also serve as an alternative source of camptothecin. Similarly, EF isolated from *Salvia abrotanoides* endemic to Iran, is a source of cryptotanshinone, the main bioactive compound of the plant (Teimoori-Boghshani et al. 2020).

(d) Plants growing in areas of great biodiversity also have the prospect of harbouring endophytes with great biodiversity. The diversity of the biological activities could be obtained by the same fungal endophyte strain isolated from different medicinal plants, increasing the opportunities to isolate a plenty of new compounds by “one strain many compounds approach” (OSMAC). *A. fumigatus* isolated from different plants proved to be synthesising a wide variety of bioactive

compounds (Silva et al. 2018; Liu et al. 2004; Ding et al. 2013). Indeed, extensive research in host-endophyte interaction should be conducted for targeting endophytes in bioprospecting

(e) The medicinal plants are an excellent source for bioprospecting endophytes. The EF such as *Acremonium*, *Alternaria, Aspergillus, Cephalosporium*, *Chaetomium, Chloridium, Choanephora, Colletotrichum, Fusarium, Gliocladium, Hypoxylon*, *Paecilomyces*, *Penicillium, Pestalotiopsis, Talaromyces*, and *Trichoderma* from different medicinal plants have been reported as a source of many bioactive compounds (Rana et al. 2019). Endophytes, which exist in plants providing a strong metabolite background might also synthetise unique secondary metabolites. Therefore, EF from medicinal plants are worth exploring and they could be a potential reservoir of novel bioactive compounds. Bioprospecting these EF has raised the expectation to meet the growing demand for plant-derived bioactive compounds (Venieraki, 2017).

The interactions between the fungus and the plant seems to serve a strong evolutionary pressure towards the synthesis of secondary metabolites by the endophytes (Schulz et al. 2002), which are usually able to improve the fitness, viability or resistance of the host plant to defend it successfully from different pests (Strobel and Daisy, 2003). Indeed, discoveries of parallel secondary metabolite production by both higher plants and plant-associated fungi are fascinating and provide a potential source of procuring adequate compounds for commercial requirements.

3.4 Fungal endophytes as sources of natural products

Natural products from fungal endophytes have a broad spectrum of biological activity and can be grouped into several categories including alkaloids, steroids, terpenoids, flavonoids, glycosides, xanthones, isocoumarins, quinones, phenylpropanoids, lignans, aliphatic metabolites and lactones (Gunatilaka et al. 2006). Investigations of these organisms - distributed worldwide from tropical forests to arctic environments indicated that they are excellent producers of compounds that can be exploited as both agrochemical and medicinal agents due to their antiviral, antibiotic, anticancer, insecticidal, immunosuppressive and antioxidant effects (Strobel and Daisy, 2003). Furthermore, it has been discovered that the produced compounds are occasionally the same as those produced by the respective hosts, which have been exclusively isolated from higher plants such as paclitaxel, podophyllotoxin, camptothecin and vinblastine (Zhao et al. 2010; Kusari et al.

2015). Furthermore, EF are able to release different types of hydrolytic enzymes to protect themselves from plant pathogens, insects and nematodes. In addition, EF produce various unique structured natural products, thereby, represent a huge reservoir offering an enormous potential for exploitation in agricultural and industrial areas (Tan and Zou, 2001). The bioactive metabolite production of EF involves mechanism such as producing compounds that stimulates the plant immune response, thereby enhancing their resistance against phytopathogens and to compete with their biological niche for colonizing (Pascale et al. 2017).

3.4.1 Secondary metabolites production of endophytic fungi

Secondary metabolites are small organic molecules (MW < 2000 Da) produced by various living organisms including plants, microbes (fungi, bacteria), marine organisms (sponges, snails) and insects. Comparing with primary metabolites such as nutrients, polysaccharides, proteins, nucleic acids and lipids, which are fundamental for survival of the organisms, secondary metabolites are not specifically responsible for survival (Sarker, 2006). Until now, tens of thousands of natural products have been identified in the world. Recently, there are a huge number of bioactive secondary metabolites identified from EF (Table 1), but still a vast number of unknown compounds are yet to be discovered and to be utilized for the benefits of mankind (Sarker, 2006).

Categorization of natural products commonly encountered include fatty acids, polyacetylenes, terpenoids (monoterpenoids, iridoids, sesquiterpenoids, diterpenoids, triterpenoids), steroids, essential oils (lower terpenoids and phenylpropanoids), phenolics (simple phenolics, phenylpropanoids, flavonoids, tannins, anthocyanins, quinones, coumarins, lignans), alkaloids, and glycosidic derivatives (e.g. saponins, cardiac glycosides, flavonoid glycosides) (Gonzalez-Mera et al. 2019). As endophytes are chemical synthesizers inside plants, they are considered as a novel resource for the aforementioned secondary metabolites for their use in medicine and agriculture (Wani et al. 2016). It could also be speculated that due to the symbiotic nature of EF with the plants, the bioactive compounds could be less toxic to the eukaryotic cells and there will not be any adverse effects of the potential drug compounds on human cells (Rajamanikyam et al. 2017). Fungi synthesize secondary metabolites for their own profit, either to get rid of their competitors or to interact with the plants under stressful environments (Rodriguez et al. 2009).

The biosynthesis of secondary metabolites mainly involves 3 important metabolic pathways such as polyketide, shikimate, and mevalonate pathways (Refaei et al. 2014) and are regulated by specific gene clusters. Polyketides are an e important class of secondary metabolites produced by EF and are synthesized in a series of condensation reactions**,** which are catalysed by polyketide synthases (PKS). There are three groups of PKS, Type I, Type II and Type III (Refaei et al. 2014; Feng et al. 2015). The two major gene clusters taking part in the secondary metabolite biosynthesis are the polyketide- and non-ribosomal peptide synthases clusters (Hoffmeister and Keller, 2007). With the current advancement in genetic engineering, numerous research groups are involved in identifying and utilizing these specific gene clusters for synthesizing native metabolites and their derivatives.

Zeilinger et al. (2016) explored the role of acetyl-CoA, mevalonate and amino acids as reaction precursors in the biosynthetic pathway for the synthesis of NRPS such as peptaibiotics, siderophores and diketopiperazines, polyketides, terpenes, pyrones, and isocyane metabolites. Acetyl-Coenzyme A and malonyl-Coenzyme A act as precursors that are further catalyzed by a group of PKS gene clusters containing domains such as ketoacyl synthase, an acyl transferase and a phosphopantetheine attachment site.

Table 1. Representative list of bioactive secondary metabolites isolated from EF.

Endophytic fungi	**Bioactive compound**	**Bioactivity**	**Reference**
***Aspergillus fumigatus* CY018**	Asperfumoid, fumigaclavine C, fumitremorgin C, physcion and helvolic acid	inhibitits *Candida albicans*	Selvakumar et al. 2018
Aspergillus niger	Lapachol	anticancer	Nirupama et al. 2011
***Cephalosporium* sp.**	Diosgenin	progesterone precursor, cholesterol lowering activity	Zhao et al. 2010
***Cephalosporium* sp. IFB-E001**	Graphislactone A	antioxidant	Selvakumar et al. 2018
Cephalotheca faveolata	Sclerotiorin	antibacterial	Selvakumar et al. 2018

Endophytic fungi	Bioactive compound	Bioactivity	Reference
Chaetomium globosum	Chaetoglobosins A and C	inhibit *Mucor miehei*	Selvakumar et al. 2018
***Cladosporium* sp.**	Brefeldin A	antifungal activity	Selvakumar et al. 2018
***Emericella foeniculicola* TR21**	Tanshinone I and IIA	cardiotonic, anti-inflammatory	Ma et al. 2011
Entrophospora infrequens	Camptothecin	anticancer	Selvakumar et al. 2018
Eupenicillium parvum	Azadirachtin A and B	natural pesticide	Kusari et al. 2012b
***F. proliferatum* BLH51**	Sanguinarine	anticancer	Wang et al. 2014
***Fritillaria ussuriensis* Fu7**	Sipeimine	antitussive and expectorant	Yin and Chen, 2008
Fusarium chlamydosporum	Kaempferol	antioxidant, anticancer	Chaturvedi et al. 2014
Fusarium oxysporum	Vinca alkaloids	anticancer	Selvakumar et al. 2018
***Fusarium proliferatum* (MTCC 9690)**	Rohitukine	antiinflammatory, immunomodulatory, anticancer	Kumara et al. 2012
Fusarium solani	Berberine	anticancer	Selvakumar et al. 2018
***Fusarium solani* LCPANCF01**	Taxol	anticancer	Selvakumar et al. 2018
***Fusarium solani* R13**	Rhein	antitumor, anti-inflammatory, antimicrobial and hemostatic	You et al. 2013
Fusarium subglutinans	Subglutinols A and B	immune-suppressants	Lee et al. 1995
Phoma glomerata D14	Fusidikactones	antifungal activity	Selvakumar et al. 2018
Penicillium oxalicum	Gymnemagenin	antidiabetic	Parthasarathy and Sathiyabama, 2014
***Penicillium* sp. Gh01**	Quercetin glycoside	anti-hypertensive, anticancer, antiinflammatory, antioxidant	Padmavathy, 2014

Endophytic fungi	Bioactive compound	Bioactivity	Reference
***Periconia* sp.**	Piperine	antimicrobial, antidepressant, antiinflammatory, antioxidative, anticancer	Verma et al. 2011
***Rhinocladiella* sp.**	Cytochalasins	anticancer, antibiotic	Strobel and Daisy 2003
Thielavia subthermophila	Hypericin	antidepressant, antiinflammatory, antimicrobial, antioxidant, antiviral	Zhao et al. 2010
T. subthermophila	Emodin	antidiabetic, antiviral, anticancer	Zhao et al. 2010

3.4.2 Secondary metabolites of endophytic fungi as antimicrobial compounds

With the emergence of new infectious diseases and multidrug resistant strains, the requirement of new antimicrobial agents is increasing, and scientific efforts have been aimed at finding metabolites with antimicrobial activities from endophytes. A diverse array of endophytic metabolites exhibited antimicrobial activity against various pathogenic microflora, and these can be used in pharmaceuticals, medicine, and agriculture (Gunatilaka et al. 2006). Terpenes are one of the largest group of compounds produced by EF which possesses antibacterial activity as guanancastepene A, guanacastepene, periconicin A, and periconicin B diterpenoids produced by an unidentified endophytic fungus isolated from *Daphnopsis americana*. Furthermore, colletotric acid produced by *Colletotrichum* sp. isolated from *Artemisia annua* showed both antibacterial and antifungal activity (Yu, et al. 2010). Furthermore, phomol, a novel antimicrobial compound has been isolated also from an endophytic fungus (*Phomopsis* sp.) isolated from the medicinal plant *Erythrina crista*. The structure of this compound was elucidated by spectroscopic methods and it proved to be a polyketide lactone (Guo et al. 2000). In endophytes, alkaloids are quite typical secondary metabolites and some of them have been shown antibacterial activity. Chaetoglobosins A and C were determined from the culture of an endophytic *C. globosum* derived from the leaves of *Ginkgo biloba*, while 3-O-methylalaternin and altersolanol, produced by the endophyte *Ampelomyces sp.* isolated from the medicinal plant *Urospermum picroides* - showed antibacterial activity against gram-positive pathogens *Staphylococcus aureus*, *S. epidermidis* and *Enterococcus*

faecalis (Aly et al. 2008). Cryptocandin A is a unique peptide, which has been considered for treatment against fungal infection in humans (Strobel, 2003). It was isolated and characterized from an endophyte *Cryptosporiopsis quercina* of *Tripterigeum wilfordii*, a medicinal plant, which is native to Eurasia (Strobel et al. 2003). In addition, jesterone and hydroxyjesterone from *Pestalotiopsis* sp. were also shown to possess antibacterial activity (Li et al. 2001).

Endophytic metabolites also possess antiviral activity, which is exemplified by cytonic acids A and B. These compounds were isolated from the culture of the endophytic fungus *Cytonaema* sp. isolated from a *Quercus* sp. and were reported as human cytomegalovirus protease inhibitors (Guo et al. 2000). Other fungal metabolites with promising antiviral activity are the novel quinone-related metabolites, xanthoviridicatins E and F, produced by an endophytic *Penicillium chrysogenum*, which inhibited the activity of HIV-1 integrase (Singh et al. 2003).

3.4.3 Endophytic fungi producing host plant secondary metabolites

As EF occupy literally millions of unique biological niches (higher plants) growing in numerous unusual environments, exciting possibilities exist as engaging in the discovery and their potential use in pharmaceuticals. Over a long period, the coexistence and evolution of endophytes with their host plants have established a special relationship significantly influencing the production of bioactive metabolites in plants (Jia et al. 2016). The communication of endophytic communities with the host plant significantly influences physiological processes of the plant. It is important to mention that some endophytic microorganisms isolated from medicinal plants produce the same metabolites as their hosts (Table **2**). This observed phenomenon leaded to the isolation of several EF producing important medicinal agents including digoxin originally described from *Digitalis lanata* (Kaul et al. 2013), ginkgolides from *Ginkgo biloba* (Cui et al. 2012), podophyllotoxin and deoxypodophyllotoxin from *Juniperus communis* (Kusari et al. 2009a), and also vincamine and vinpocetine from *Vinca minor* (Yin and Sun 2011). The endophytic fungus, *Thielavia subthermofila* strain was able to produce hypericin and emodin *in vitro* (Kusari et al. 2008).

Bioprospecting EF for host associated metabolites would not only reduce the need to harvest slow growing and possibly rare plants**,** but also preserve the world's ever-diminishing

biodiversity. Furthermore, it is recognized that a microbial source of a valued product may be easier and more economical to produce, effectively reducing its market price (Strobel, 2003; Kusari et al. 2009a).

Table 2. Host medicinal plants and their EF producing host metabolites.

Host plant	Endophytic fungi	Compound	Reference
Catharantus roseus	*Fusarium oxysporum*	vinblastin and vincristine	Palemp et al. 2015
Huperzia selago	*Penicillium griseofulvum, Aspergillus flavus, Shiraia sp.,*	huperzine	Higgin et al. 2017
Taxus baccata	*Fusarium redolens*		Garyali et al. 2013
	E. nigrum	Paclitaxel, baccatin	Salehi et al. 2019
	Monochaetia sp.,		
	Pestalotia bicilia		
Vinca minor	Unidentified fungi	vincamine, vinpocetine	Yin et al. 2011
Hypericum perforatum	*T. subthermophilia*	hypericin	Kusari et al. 2009
Digitalis lanata	*Alternaria* spp, *Penicillium* spp., and *Aspergillus* spp.	digoxine (glycoside)	Kaul et al. 2013
Ginkgo biloba L.	*Fusarium oxysporum* SY0056	glinkolide B (terpenoid lactone)	Cui et al. 2012

Host plant	Endophytic fungi	Compound	Reference
Solanum nigrum L.	*Aspergillus flavus*	solamargine (alkaloid)	El-Hawary et al. 2016

3.4.4 Hypericin and emodin, host plant secondary metabolites involved in this study

Hypericin (4,5,7,4′,5′,7′-hexahydroxy-2,2′-dimethylnaphtodianthrone) is one of the medicinally important polyphenolic compounds as it is proved to be possessing antidepressive, antitumor and antiviral properties and is also used in photodynamic therapy for the detection and treatment of tumor cells (Karioti and Bilia 2010). This medically important phenanthoperylene quinone is found in some species of the genus *Hypericum*, particularly in *Hypericum perforatum* L. commonly called as St. John's wort (Banks et al. 1976). Due to the broad-spectrum pharmacological importance of hypericin, it has been intensively studied in recent decades (Wölfle et al. 2014). However, besides *Hypericum* species, hypericin has also been found in certain basidiomycetes belonging to the *Dermocybe* genus (Garnica et al. 2003; Dewick, 2009) as well as in a filamentous fungus (Table 2), which was isolated as the endophyte of *H. perforatum* (Kusari et al. 2008).

Emodin is a well-known medicinal herb product possess antibacterial and anti-cancer activity (Dong et al. 2016), however, according to previous studies emodin has been identified firstly from *Cortinarius sanguineu*s (formerly known as *Dermocybe sanguinens*) as a pigmented metabolite in 1925 (Kögl and Postowsky, 1925). This compound has since been detected as a product of *Cladosporium fulvum* (Agosti et al. 1962) and *Aspergillus* species including *Aspergillus wentii* (Wells et al. 1975), *Aspergillus ochraceus* (Lu et al. 2010) as well as *T. subthermophila* (Kusari et al. 2008).

The biosynthesis of hypericin is not yet clarified experimentally in plants, but it is presumed to follow the polyketide pathway containing subsequent reactions started with the condensation of seven molecules of malonyl-CoA with an acetyl-CoA (Figure 2). After that, the resulted octaketide chain undergoes both cyclization and decarboxylation reactions to form emodin anthrone, which is oxidized to emodin probably by the enzyme emodinanthrone-oxygenase and then, a condensation

reaction yields a dianthrone leading to the formation of protohypericin and finally of hypericin (Karioti and Bilia, 2010). This biosynthetic pathway is generally accepted and genes encoding the corresponding enzymes were already analysed via next generation sequencing technology (Soták et al. 2016). Bais et al. (2003) described an enzyme, *hyp-1*, in *H. perforatum* cell cultures, which seems to be specifically involved in the direct conversion of the emodin to hypericin *in vitro*. Few years later, Michalska et al. (2010) failed to dimerize emodin to hypericin using *hyp-1* as the biocatalyst, suggesting that *hyp-1* does not participate in hypericin synthesis, but it might act as a transporter. Furthermore, studies proved that *hyp-1* gene is expressed in all investigated *Hypericum* species regardless of their hypericin production, hence proposed that *hyp-1* gene is not a limiting factor in the hypericin production in *Hypericum* species (Kosuth et al. 2011).

The spatial distribution of the chemical members of the biosynthetic pathway *in planta* was determined with desorption electrospray ionization mass spectrometry imaging, (Thunig et al. 2011) and matrix free UV-laser desorption/ionization mass spectrometric imaging (Hölscher et al. 2009) as well as by matrix-assisted laser desorption/ionization high-resolution mass spectrometry (MALDI-HRMS) techniques (Kusari et al. 2015). In these examinations, hypericin was localized in the dark glands on the leaves of *H. perforatum,* but the proposed precursor, emodin anthrone, could not be visualized. Due to its high reactivity, emodin anthrone can be instantaneously converted to emodin by oxidation. However, the other main proposed precursor, emodin was not only accumulated in the dark glands, but was also detected in significant amounts outside the glands suggesting that the presumed site of hypericin biosynthesis is in the cells adjacent to these gland structures from emodin (Kusari et al. 2015).

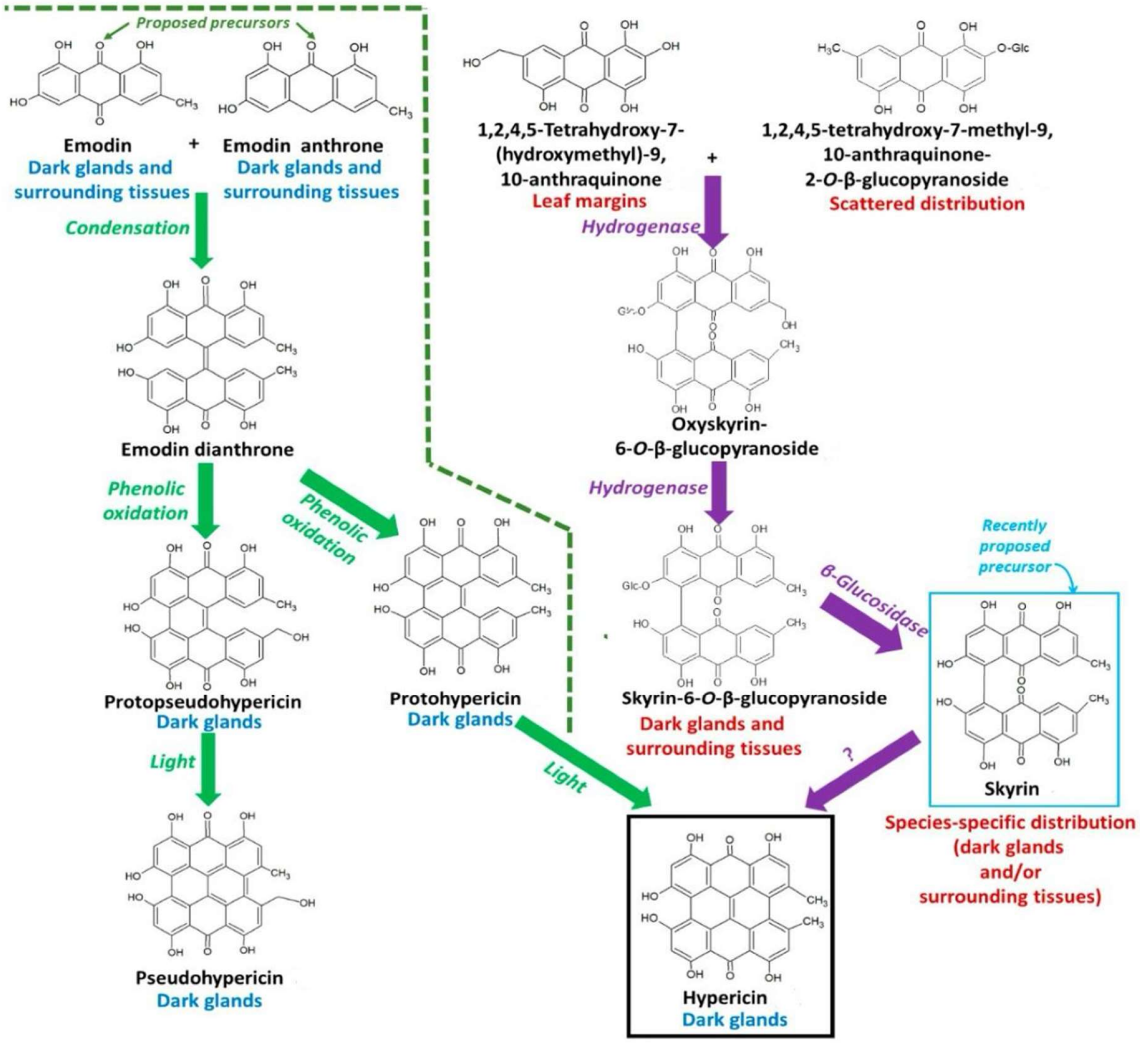

Figure 2. The proposed biosynthetic pathway of hypericin (Revuru et al. 2020).

Another study proposed a different biosynthetic pathway in *Hypericum* species, which involves skyrin as an intermediate (Kimáková et al. 2018). The same group, in different study found that most of the EF isolated from *Hypericum* species are synthesizing skyrin apart from emodin (Figure 2) (Revuru et al. 2020).

Recently, the same research group established this hypothesis by reporting the spatial distribution of skyrin and also localized other compounds skyrin-6-O-β-glucopyranoside, 1,2,4,5-tetrahydroxy-7-methyl-9,10-anthraquinone-2-O-β-glucopyranoside and 1,2,4,5-tetrahydroxy-7-(hydroxymethyl)-9,10-anthraquinone**,** which are considered as the precursors of skyrin in the

leaves of *Hypericum* species using MALDI-HRMS imaging (Revuru et al. 2020). Finally, it can be concluded that detailed genetic studies are further required to identify the candidate genes correctly and corroborate the exact biosynthesis of hypericin in plants.

3.5 Plants selected in the current study and their reported fungal endophytes

Hungary is located in central Europe and belongs to the eco-region of Pannonian mixed forests and has a promising phyto-geographical condition. Yet there is a lack of data on the endophytic fungal communities in this region. Only a few studies have been carried out enlisting the endophytic community in Hungary (Knapp et al. 2012)

In our study 4 plants were selected to investigate EF producing novel bioactive metabolites.

3.5.1 Hypericum perforatum

The genus *Hypericum* includes almost 500 species among which *Hypericum perforatum* is the best known for its traditional medicinal value. *Hypericum perforatum* L. (common St. John's wort) is a widely distributed medicinal herb, which has been used over the past 2000 years for its diverse healing properties (Butterweck, 2003). The genus *Hypericum* belongs to the Hypericaceae family involving almost five hundred species (Crockett and Robson, 2011). Most of them are able to synthetize metabolites possessing antioxidant (Silva et al. 2005), anticancer (Agostinis et al. 2002), antidepressive (Butterweck, 2003) and antiviral (Birt et al. 2009) as well as antifungal and antibacterial effects (Kusari et al. 2008).

Studies have reported that *Hypericum* species constitute several napthodianthrones, which include naphthodianthrone derivative hypericin (2,2'-dimethyl-4,4',5,5',7,7'-hexahydroxy-mesonaphtodianthrone), that is a potential lead candidate molecule for future therapeutics (Karioti and Bilia, 2010).

Kusari et al. (2008) first isolated EF from *H. perforatum* and found the host metabolite producing ability of one strain. Later Zhang et al (2014) isolated 21 EF species from *H. perforatum* in China. The dominant species were found to be *Fusarium sp., Mucor sp., Aspergillus sp., Xylaria sp. and Hypocrea sp.,* and they also reported the antimicrobial effect of these strains.

3.5.2 Juniperus communis

Juniperus communis is a bush or small evergreen tree which has been commonly referred to as herbal medicine in ancient times. *Juniperus communis L.*, which is known as the 'common juniper', This is one of the most prevalent species of European conifers and is native to Europe, South Asia, and North America (Farjon and Filer, 2013). It belongs to the Cupressaceae family. The main chemical constituents of *J. communis* L. are β-pinene, apigenin, sabinene, β-sitosterol, campesterol, limonene and cupressuflavone.

It contains various chemical constituents including flavonoids, volatile oil, coumarins and therapeutically important anticancer lignans, podophyllotoxin and deoxypodophyllotoxin (Hartwell et al. 1953). Many essential extracts from its twigs, leaves, and berries (the blue-black seed cones) have been used as anti-diarrheal, anti-inflammatory, astringent, disinfectant gastrointestinal agents, or against urinary tract infections, dermatitis, or as a diuretic. The wood has even been shown to be suitable for artificial bone implants (Gross and Ezerietis. 2003). The twigs, leaves, and especially the berries represent an important food source for several small and large animals and even humans for culinary purposes and preparation of alcoholic drinks (Vichi et al. 2008)

Generally, the dried needles called savin, or the derived oil of *Juniperus* species have been used by native people to cure leprosy, ulcer and also uterine polyps (Bais et al. 2014).

Previous studies had been carried out to isolate and characterize EF harboured in *Juniperus* plants sampled from the natural populations in Dortmund and Haltern, Germany, and Jammu and Kashmir, India. This resulted in the discovery of a deoxypodophyllotoxin-producing endophytic fungus harboured in *J. communis* (Kusari et al. 2009a). The lignans podophyllotoxin and deoxypodophyllotoxin are secondary metabolites with a wide variety of biological activities and show efficient pharmaceutical applications in cancer therapy (Kusari et al. 2012). The EF isolated from *Juniperus* trees such as *Penicillium, Aspergillus* were also found to be exhibiting antimicrobial activity (Gherbawy and Elhariry, 2016).

3.5.3 Artemisia asiatica

The *Artemisia* genus consists of around 400 species and these are one of the most important sources of medicinal compounds. A review on the chemical compounds of 15 *Artemisia*, reported 839 compounds, which mainly consists of terpenoids, flavonoids, coumarins, caffeoylquinic acids, sterols, and acetylenes (koul et al. 2018).

Among the *Artemisia* species, *A. annua* is the most known due to its artemisinin content, which is an important antimalarial drug (Weathers et al. 2011). Liu et al. identified 14 fungal endophytes in *A. annua* (Liu et al. 2001), which produced antagonistic compounds against four phytopathogens. Another study showed the bioactive potential of *A. annua* EF such as *Aspergillus sp.* and *Cephalosporium sp.* that were proved to be having the highest antibacterial activity (Zhang et al. 2017).

Most of the EF isolated from *A. annua* were investigated for their role as an elicitor in the production of artemisinin. There have been limited studies conducted on bioprospection of EF of *Artemisia* species and its EF communities have been proved as a source of 27 novel compounds and 22 have already been characterized (Cosoveanu and Cabrera 2018).

A. asiatica is also known as mug wort. This is a perennial plant and abundantly found in the northern temperate regions of Asia, Europe and North America. This species is widely known for its medicinal properties and their essential oil is commonly used in medicine and food products. *A. asiatica* has been proven to be effective against diseases such as hanol and indomethacin-induced gastric injury (Oh et al. 2005), acetaminophen- and carbon tetrachloride-liver dysfunction (Ryu et al. 1998) and cerulein-induced pancreatitis (Ahuja et al. 2018). There are 22 known phytochemical compounds that have been identified from *A. asiatica* including flavonoids, coumarins, terpenes, sesquiterpene lactones, monoterpenes, guaianolidem secoguianolide, lignans, phenylpropanoids and steroids (Hajdu et al. 2014). Eupatilin and jaceosidin flavonoids are also identified from this plant and are known to possess wide bioactivities such as anticancer, anti-microbial, anti-inflammatory and antioxidative effects (Cheong et al. 2011; Choi et al. 2011a; Choi et al 2011b.; Lee et al. 2008). A recent study shows that the ethanolic extract of *A. asiatica* could have skin-protective remedy with anti-photoaging, anti-apoptotic, skin remodelling and anti-melanogenesis properties (Jeong et al. 2014). Despite the broad-spectrum bioactivity of *A. asiatica,*

and the fact that its EF community has not been investigated, we have chosen this plant for our investigations.

3.5.4 Mosses

Most of the studies on endophytes have been focused on vascular plants. Despite the wide diversity and significance of non-vascular plants especially in boreal forests, they remain under investigated in terms of their endophytic community. Mosses are non-vascular plants, that belong to the division of Bryophyta. They are small non-flowering plants**,** which absorb essential nutrients through their leaves (MacKinnon et al. 2004). We chose mosses for our investigations based on the rationale that they are most distinct in their physiology and ecology (Cox et al. 2014; Wickett et al. 2014).

Mosses mostly flourish in a vast variety of habitats that range from the cold arctic environment to hot deserts, sea-levels and alpines (Higgins et al. 2007.); Malcolm and Malcolm, 2000).They are ubiquitous and play an important role in regulating moisture and temperature in ecosystems. They are also known as microhabitats of microbes and small arthropods (Staddon et al. 2010). Although approximately 14,000 moss species exist, they have not been well studied for their microbiome population.

Mosses have been investigated for their endophytic bacterial community and a study reports that mosses are habited by with nitrogen-fixing, phosphorus-solubilizing and IAA-secreting bacteria that play a key role in promoting their growth (Lan et al. 2020). There are several studies about its endophytic bacterial community (Lan et al. 2020; Shcherbakov, 2013) and it has also been reported that the endophytic bacterial community differs in four mosses collected from the same soil crusts.

In addition, a great phylogenetic diversity of endophytes has been found in bryophytes such as liverworts, moss in boreal, temperate and tropical forests (Davis et al 2003; Davis and Shaw, 2008; Kauserud et al. 2008; U'Ren et al. 2010). In addition to this study bryophytes in the Antarctica have been investigated for their endophytic fungal community. This study shows the cold adaptation of EF from three different bryophytes (Zhang et al. 2013). Due to the limited investigation regarding the EF of mosses, these plants were also selected for our study.

4 OBJECTIVES

The aim of this work was to isolate, identify as well as evaluate and compare the bioprospects of fungal endophytes harboured in Hungarian plants. Furthermore, to provide fundamental insights into the host metabolite producing abilities of EF and reveal the antimicrobial activity of the secondary metabolites produced by the examined endophytic community.

The main objectives are,

1. Screening for host metabolite producing EF from the *H. perforatum.*
2. In the case of finding host metabolite producer strains, detailed investigation of the host metabolite producing EF regarding the taxonomy, yield of the metabolites and dependence of the production on certain cultivation conditions.
3. Isolation and identification of EF from *J. communis*, *A. asiatica* and several mosses and evaluation of their biodiversity.
4. Determination of antimicrobial activities of metabolites extracted with different organic solvents from the ferment broth and mycelia of isolated EF.

5 MATERIALS AND METHODS

5.1 Culture media used in this study

Potato Dextrose Agar – PDA (VWR International Ltd., Debrecen)

Potato Dextrose Broth– PDB (VWR International Ltd., Debrecen)

Defined Medium (Velmurugan et al 2010) – DM (for 1L):

30 g glucose, 1.0 g $(NH_4)_2SO_4$, 0.5 g $MgSO_4 \cdot 7H_2O$, 1.4 g K_2HPO_4, 0.6 g KH_2PO_4, 0.8 mg $ZnSO_4 \cdot 7H2O$, 0.8 mg $FeCl_3 \cdot 6H_2O$, 0.8 mg $NaMoO_4 \cdot 2H_2O$, 0.4 mg $MnSO_4 \cdot 2H_2O$, 0.08 mg $CuSO_4 \cdot 5H_2O$ (pH=5.6)

Czapek-Dox Broth (Me´ndez et al. 2011) – CDB (for 1L):

30 g sucrose, 3.0 g $NaNO_3$, 1 g $K_2HPO_{4,\ 0.5}$ g $MgSO_4 \cdot 7H_2O$, 0.010 g $FeSO_4$ (pH=7.3)

Malt extract broth (Mapari et al. 2008) – MEB (for 1L):

17 g malt extract, 3 g mycological peptone (pH=5.4)

Luria-Bertani broth – LB (for 1L):

10 g tryptone, 5 g yeast extract, 5 g NaCl

Yeast extract peptone dextrose broth – YPD (for 1L):

20 g peptone, 10 g yeast extract, 20 g glucose

Nutrient broth – NB (for 1L): 1 g peptone, 15 g NaCl, 6 g yeast extract

5.2 Collection of plant samples

Fresh, healthy aerial parts of the selected plants were collected in late Autumn in 2015, 2016 and in 2017, where GPS coordinates were recorded (Table S1).The collected plants were *Hypericum perforatum* and *Juniperus communis. Artemisia asiatica* and different mosses were provided by the Department of Pharmacognosy, University of Szeged. All plant specimens have been identified and authenticated by experts. Collected specimen was placed in a sealed plastic bag and was

labelled with the number and date of collection and stored at 4 °C until processing.

5.3 Isolation of plant endophytes

Isolation of EF from plant parts was done according to the method described by Gariyali with minor modifications (Garyali, 2013). The plant materials were rinsed in running tap water to remove dust and debris and the specimens were cut into small segments of about 0.5 to 1 cm in length using a sterile blade. In the case of *J. communis*, the leaf, twig, root and cone parts were separated, and these parts were examined for their fungal endophyte content.

The plant segments were surface sterilized to kill the epiphytic microorganisms by sequentially immersing the plant material in 70% ethanol for 60 s, washing with sterile distilled water and then, steeping in 0.01% mercuric chloride (VWR International Ltd., Hungary) for 30 sec. Finally, the specimens were washed again with sterile distilled water 2-3 times and then allowed to dry on a sterile blotting paper. Each segment was placed onto the surface of PDA medium supplemented with ampicillin (50 µg/mL, Merck Ltd., Hungary) in a Petri dish. All plates were incubated at 25 °C for 5-10 days and were checked daily for the growth of fungal colonies. Pure isolates were obtained by picking up individual colonies from the plates and transferring them onto a fresh PDA medium, where they were incubated at 25 °C for 10 days. Each fungal culture was checked again for purity and transferred separately to PDA slants and maintained at 4 °C and this generation (3rd) of the isolates were deposited into the Szeged Microbiological Collection (SZMC, Hungary, http://szmc.hu/).

5.4 Molecular identification of endophytic fungi

For DNA isolation, fungal isolates were grown in PDB for 5 days at 25℃. Isolation of the genomic DNA from the mycelia was performed using E.Z.N.A. Fungal DNA Kit (Omega Bio-tek) according to the manufacturer's instructions. The internal transcribed spacer (ITS) region of the rDNA was amplified using the primers ITS1 and ITS4 as described previously (White et al. 1990). Sequencing of the amplified DNA fragments was performed on an ABI 373A DNA sequencer (Applied Biosystems Inc., USA) using dye dideoxy terminator reaction chemistry. The sequences were first analyzed by BLAST similarity search at the website of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/BLAST) and the species were identified

based on their identity values (>97%). Identification of the SZMC 23773 strain was also reinforced using the online software (www.isth.info) TrichOkey 2.0 (Druzhinina et al. 2005).

5.5 Targeted screening of host metabolite production of *H. perforatum* isolates

5.5.1 Preparation of metabolite extracts

Isolated EF were cultured for 7 days at 25°C in 50 mL PDB medium. The extraction was carried out according to a description by Kusari et al. with minor modifications (Kusari et al. 2008). The mycelia were separated from the broth by filtration through a cheese cloth and overnight dried in an oven until constant weight, which was recorded. Then 25 mL distilled water was added to the dry material, which was then sonicated for 20 min after the addition of an aliquot of liquid nitrogen to maintain the chilled condition. This aqueous solution was extracted then three times, first, with 25 mL ethyl acetate (EtOAc) and then, with 25 mL chloroform-methanol (4:1), and the extracts obtained with the same solvent were pooled. Fifty mL of the ferment broth was also extracted three times sequentially with 50–50 mL of EtOAc and chloroform-methanol (4:1), respectively, and the extracts were also pooled. The organic solvents from each pooled extract were removed by a rotary evaporator (IKA HB10 basic, VWR International Ltd., Hungary) in vacuum at 30°C. The resulted four dry samples per each isolate were stored at -20°C and resuspended in 1 mL of HPLC grade methanol (VWR International Ltd., Hungary) prior to use.

5.5.2 HPLC-UV analysis

The applied analytical method was based on the description of Li and Fitzloff, with slight modifications (Li and Fitzloff, 2001). The extracts were analyzed by modular HPLC system (Shimadzu, Japan) equipped with a CBM-20A system controller, a DGU-14A degasser, an LC-20AD binary pump, a SIL-20A autosampler, a CTO-10ASvp column thermostat and an SPD-10Avp UV-VIS detector, which was controlled by ClassVP 6.2 software. The peaks were detected at a wavelength of 436 nm. The mobile phase consisted of water containing 20% methanol (A, WVR International Ltd., Hungary) and acetonitrile (WVR International Ltd., Hungary) containing 10% methanol (B) and both were supplemented with 0.5% trifluoroacetic acid (Merck Ltd., Hungary). Separations were performed on a Phenomenex Gemini 250 × 4.6 mm, 5 μm reversed phase column (GenLab Ltd., Hungary) coupled with Phenomenex C18 guard column (GenLab

Ltd., Hungary) with a flow rate of 1 mL/min using a gradient program started with 10% B, and reached to 70% B until 10 min, to 90% until 15 min and to 25 min until 100%, which was kept until 60 min and reduced to initial eluent ratio and held to pressure stabilization. The total analysis time was 65 min. The injection volume was 5 µL. The calibration was done with serial dilution of hypericin and emodin standards (Merck Ltd. Hungary) in the range of 250 µg/mL to 7.8 µg/mL based on the retention times of hypericin (32.8 min) and emodin (16.9 min). The quantity of hypericin and emodin present in the samples were quantified using the equations y = 0.000142788 x—5.07 and y = 0.0000808111 x—4.66, respectively, while the r values were 0.998 and 0.999 for hypericin and emodin, respectively.

5.5.3 HPLC-HRMS and HRMS/MS analysis

The identity of hypericin and emodin was confirmed by a Thermo QExactive Plus high-resolution mass spectrometer (Thermo Scientific, USA), which was coupled to a Waters UPLC I-Class System (Waters, USA) consisting of a binary pump, a column manager and a fixed loop auto sampler. The separations were performed by using a Phenomenex Kinetex XB-C18 column (2.6 µm, 2.1 × 50 mm, 100 Å) (GenLab Ltd., Hungary) with water (A) and acetonitrile (B) eluents containing 0.1% formic acid with a flow rate of 0.5 mL/min at 40°C. Samples and standards were analyzed using a gradient program as follows: from 5% B linear gradient to 95% B over 10 min and after 95% B isocratic for 2.5 min, the system returned to its initial condition (5% B) within 0.1 min and was equilibrated for 2.4 min. The mass spectrometer was operated in data dependent MS2 mode with negative electrospray ionization (ESI) (number of precursors: Top 5; scan range 100–1500; dynamic exclusion: 10 sec; 1 exclude isotopes: on; stepped NCE: 30, 50, 80) with nominal mass resolving power of 60 000 at *m/z* 200 with a scan rate of 1 Hz with automatic gain control to provide high-accuracy mass measurements within 2 ppm. Nitrogen was used as sheath gas, and as the collision gas. The source parameters were the followings: spray voltage (-): 2500.00V, capillary temperature (-): 300.00°C °C, sheath gas (-): 55.00 arbitrary units, auxillary

gas (-): 15.00 arbitrary units, spare gas (-): 5.00 arbitrary units, max spray current (-): 100.00 µA, probe heater temp. (-): 450.00 °C, S-lens RF level: 50.00 arbitrary units.

5.5.4 Antibacterial assay

The standard compounds, hypericin and emodin (100 µg/µL) and the methanolic solution of the extracted samples of both mycelia and ferment broth were tested using the microdilution method based on the guideline of the Clinical and Laboratory Standards Institute (Clinical and Laboratory Standards Institute (CLSI) 2015) against bacterial strains including *Escherichia coli* (SZMC 0582), *Pseudomonas aeruginosa* (SZMC 21886), *Staphylococcus aureus* (SZMC 14532), *Bacillus subtilis* (SZMC 14624) *Micrococcus luteus* (SZMC 6207) and *Streptomyces albus* (SZMC 0282), which were obtained from the Szeged Microbiological Collection (SZMC, http://www.wfcc.info/ccinfo/collection/by_id/987, Szeged, Hungary). The suspensions of each bacterium were prepared from overnight broth cultures cultivated in NB broth at 37 °C and the concentrations of the suspensions were adjusted to 4 x 10^5 cells/mL. The extracts resuspended in methanol were diluted with water to reach the methanol content up to 10%. The 96-well plates were prepared by dispensing into each well 100 µL of NB containing the bacterial cells and 100 µL of extracts and incubated for 24 h at 37 °C. The mixture of 100 µL NB and 100 µL extracts were used as the blank sample for the background correction, while 100 µL of bacterial cultures supplemented with 100 µL of 10% methanolic solvent or 100 µg/mL ampicillin (Merck Ltd., Hungary) solution was applied as the positive and the negative controls, respectively. Absorbances were measured at 620 nm after 1 and 24 hours of incubation and inhibition (%) was calculated as the percentage of the positive control after the blank correction.

5.5.5 Phylogenetic Analysis of Producer strains

In the case of *Alternaria*, the ITS sequences of the producer strains were aligned to those of the ex-type and representative strains (Woudenberg et al. 2013; Chen et al. 2017). The table of the used species and the GenBank identifier of the applied sequences are given in Online Resource 1. The CLUSTAL_X software (Thompson et al. 1997) was applied to perform the alignment. The phylogenetic tree was constructed with the neighbor-joining method using 1,000 bootstrap replicates (Saitou and Nei, 1987). The percentage of replicate trees, in which the associated taxa

clustered together in the bootstrap test (1000 replicates), were positioned next to the branches (Felsenstein, 1985). The evolutionary distances were computed using the p-distance method (Nei and Kumar, 2000) and were given in the units of the number of base differences per site. The phylogenetic analysis of *Alternaria* species involved altogether 64 nucleotide sequences using the outgroup rooting method, with strain *Stemphylium herbarum* CBS 191.86 (KC584239) designated as the outgroup. All ambiguous positions were removed for each sequence pair and there were 368 positions in the final dataset. The phylogenetic analyses and the tree construction were conducted in MEGA7 (Kumar et al. 2016).

5.5.6 Statistical analysis

The statistical analysis was performed using the GraphPad Prism version 7.0 for Windows (GraphPad Software). To compare the inhibition effects of hypericin, emodin and the fungal extracts on the bacterial strains, the one-way analysis of variance (ANOVA) was used and $p<0.05$ was accepted as statistically significant.

5.6 Effect of different cultivation parameters on the production of hypericin and emodin

5.6.1 Hypericin and emodin production under dark and light conditions

The fungi *Epicoccum nigrum* (SZMC 23769) and *Alternaria* sp. (SZMC 23771) were inoculated into 100 mL Erlenmeyer flask containing 50mL of PDB from the parent axenic culture. These flasks were completely covered by aluminium foil and incubated at 28 ± 2°C with shaking (120 rpm) on a rotary shaker for 7 days in dark condition. A similar set of cultivations was prepared simultaneously and processed parallelly in the same way, but under complete light condition. Three replicates of each experiment set were performed.

5.6.2 Hypericin and emodin production on different media

To investigate the effects of the media on the host metabolite production, the producer strains were cultivated in 100 mL Erlenmeyer flasks containing 50 mL of PDB, MEB, DM and CDB. Each flask was inoculated with one mycelial plug cut from the edge of 1-week-old fungal colonies and incubations were carried out for 7 days at 150 rpm under light condition. Biomass production in each medium was investigated and the samples were prepared according to the 5.5.1

chapter and host metabolite content was measured as described in 5.6.5 in triplicates and mean values were calculated. All experiments were performed in triplicates.

5.6.3 Sub-cultivation studies on the production of host metabolites

Seven generations of one mycelial plug cut from the edge of 1-week-old fungal colonies of *E. nigrum* (SZMC 23769) and *Alternaria sp.* (SZMC 23771) were inoculated in 50 mL of PDB, MEB, CDB and DM and cultivated for 7 days at 28 ± 2°C with shaking (120 rpm). The samples were then prepared according to 5.5.1 chapter and measured as described in 5.6.5 to quantify the hypericin and emodin amount. All experiments were performed in triplicates.

5.6.4 Testing the effects of elicitors on hypericin production

To the test the influence of different elicitors on the hypericin production the following experimental setups were applied:

a) Two grams of *H. perforatum* tea leaves were mixed with 100 mL of sterile distilled water and steeped overnight. Then 25 mL of the filtered tea was added to 25 mL of PDB.

b) Two grams of *H. perforatum* tea leaves were mixed with 100 mL of sterile distilled water, steeped overnight and filtered. The PDB medium was then prepared 50 mL of this tea instead of water.

c) A hundred milligrams of sterilized and crushed leaves and stems were added directly to 50 mL of PDB.

d) The fermentation medium was supplemented with emodin in 50 µg/mL, 100 µg/mL concentration levels.

e) Aliquots of filtered broth medium (1 mL and 2 mL) of SZMC 23769 inoculated with the 3rd fungal generation were made up to 50 mL with PDB.

In the case of each setup the mycelial plug of 7th Sub-cultivation of SZMC 23769 was inoculated into the medium and cultivated for 7 days at 28 °C with shaking (120 rpm). After 7 days the mycelia were sub cultured into the fresh PDB medium for 7 days at 28 °C with shaking (120 rpm). Then the extraction was done according to 5.5.1 chapter and the hypericin quantity was

measured as described in 5.6.5. All the experiments were performed in triplicates.

5.6.5 HPLC-MS/MS analysis

The metabolite extraction was carried out like the aforementioned method described in 5.5.1. The identity of hypericin and emodin was confirmed by a LC-MS system (Shimadzu, Japan) equipped with LC-20ADXR pump, DGU-20A5R degasser, SIL-20AXR autosampler, CTO-10ASVP oven and a TSQ Quantum Access (Thermo Scientific, USA) mass spectrometer. The separations were performed by using a Phenomenex Gemini-NX C18, 50 mm x 2mm, 3µm (GenLab Ltd., Hungary) column. The mobile phase consists of A and B eluents, where A contained MeOH (VWR International Ltd., Hungary), MeCN (VWR International Ltd., Hungary) and water in the ratio of 1: 1: 8 with 0.1% acetic acid and 5 mM of ammonium acetate, while B constituted of MeOH and MeCN in the ratio of 1:1 containing 0.1% acetic acid and 5 mM ammonium acetate. The flow rate was 0.3 mL/min at 40°C. Samples and standards were analyzed using a gradient program, which started at 50 % B, and it rose linearly to 87% in 3 min and then to 95% in 0.1 min and held for 3.6 minutes. In 0.3 minutes, B solvent rose to 98% and was held for 2.5 min. The mobile phase composition returned to the initial conditions in 0.2 min and was held for 5 min for re-equilibration resulting in a total runtime of 13.7 minutes. Mass spectrometric analysis was conducted using TSQ Quantum Access (Thermo) mass spectrometer in multiple reaction monitoring mode. The instrument was equipped with a heated electrospray ionization (HESI) source which operated in negative ionization mode. The operating conditions were as follows: electrospray voltage 4000 V, sheath gas pressure 60 arbitrary units, ion sweep gas pressure 2 arbitrary units, auxiliary gas Pressure 15 arbitrary units, vaporizer temperature 379 °C, capillary temperature was maintained at 250°C and collision pressure was continuously regulated at 2.6 m Torr (Ar). The target ion and collision energy were *m/z* 269.87→226.15, 28 V and *m/z* 503.20→405.620, 56 V for emodin and hypericin respectively.MS/MS transition and collision energy for confirmation were *m/z* 269.87→242.14 28 V for emodin and *m/z* 503.20→433.54, 56 V. for hypericin. The total scan time was 0.015 sec.

5.7 Biodiversity mapping of endophytic fungi of *A. asiatica*, *J. communis* and mosses

5.7.1 Calculating Isolation rate and diversity index

The Isolation rate (IR) of EF was calculated as the total number of tissue segments infected by fungi divided by the total number of tissue segments incubated (Kumar and Hyde, 2004) The relative abundance was calculated as the number of isolates of a taxon divided by the total number of isolates of all taxa, and the fungal richness was defined as the number of fungal species in a sample.

The diversity of EF isolated from three plants were evaluated using the Shannon–Weiner Index (*H'*), Simpson's Dominance D), evenness Index (*J*), and Margalef richness index (Hoffman et al. 2008; Suryanarayanand et al. 2000; Kusari et al. 2012). All the diversity indexes were calculated plant wise and also tissue wise to analyse the host and tissue specificity of EF.

5.7.2 Statistical analysis

Statistical analyses for biodiversity calculations were carried out in R 3.5.2. The diversity indexes were calculated using Vegan package from R 3.5.2. One-way analysis of variance (ANOVA) was carried out to test the effect of plant species or tissue type (stem and root and leaf) on the species richness of EF. Post hoc Tukey's Honest Significant Difference tests were performed to observe the significant differences among the plant species or tissue types at $P < 0.05$ level.

5.8 Screening of bioactive metabolite producing endophytic fungi

5.8.1 Secondary metabolite extraction

Isolated EF were cultured for 7 days at 25°C in 50 mL PDB medium. Then the mycelia were separated from the broth by filtration through a cheese cloth and overnight dried in an oven until constant weight, which was determined. Then 25 mL distilled water was added to the dry material, which was then sonicated for 20 min after the addition of an aliquot of liquid nitrogen to maintain the chilled condition. After that the extraction of the aqueous samples was done with the mixture of 25 mL of chloroform and MeOH (4:1) and extraction was repeated for three times. The ferment broths were extracted three times sequentially with 50–50 mL of hexane, EtOAc and

chloroform, respectively, and both extract series were pooled. The organic solvents were removed by a rotary evaporator (IKA HB10 basic, VWR International Ltd., Hungary) in vacuum at 30°C from each pooled extract including EtOAc, chloroform as well as chloroform and MeOH (4:1) fractions. The resulted four dry samples per each isolate were stored at -20°C prior to use.

5.8.2 Antimicrobial activity assay

For testing the antibacterial potential of the crude extracts, 400 µL of the methanolic extracts were transferred into new Eppendorf tubes and were dissolved in 1 mL 10% MeOH after the evaporation. These extracts were tested against two Gram-negative bacteria *E. coli* (SZMC 6271) and *P. aeruoginosa* (SZMC 23290) and two Gram-positive bacteria *S. aureus* (SZMC 14611) *and B. subtilis* (SZMC 0209) and two yeasts *C. albicans* (SZMC 1533) and *C. krusei* (SZMC 1352*)*, all of which were obtained from the SZMC, Szeged, Hungary. For the assay, the suspensions of the microbes were prepared from overnight cultures that were cultivated in a ferment broth (bacteria-LB; yeast-YPD) at 37°C, and their concentrations were set to 4×10^5cells/mL with sterile media. Then, 96-well plates were prepared by dispensing 100µL of suspension containing the bacterial or yeast cells, 100µL of the extract which is dissolved in 10% of MeOH added into each well, which were then incubated for 24 h at 37°C. The mixture of 100µL of broth and 100µL of 10% MeOH was used as the blank sample for background correction, while 100µL of the microbial suspension supplemented with 100µL of 10% MeOH was applied as the negative control. The positive control contained ampicillin (100 µg/mL, Merck Ltd., Hungary) for bacteria and nystatin (10 µg/mL, Merck Ltd., Hungary) for fungi. The inhibitory effects of each derivative were spectrophotometrically determined at 620 nm after incubation, and the inhibition rate was calculated as the percentage of the positive control after blank correction.

5.8.3 Antifungal activity against phytopathogenic fungi

To determine the potential antifungal activity of the fungal extracts against plant pathogenic fungi, agar well diffusion assay was carried out. Evaporated samples of crude extracts were dissolved in 1 ml 10% MeOH. four holes were bored into PDA plates in diameter of 8 mm same distances around to centre of the plate. Then precultured (25 °C, 7 days) *Fusarium culmorum* (SZMC 11039) and *Rhizoctonia solani* (SZMC 21048) strains were placed in the centre of plates

with agar plugs. After that, 100 µl of samples was applied into each well. As solvent control, 10% MeOH was used. The mycelial plug inoculated without any extracts was used as a control. Antifungal activity of the samples was determined by the size of the inhibition zone.

6 RESULTS AND DISCUSSIONS

6.1 Selection of plants

The medicinal plants were collected from the southern Hungarian areas. This set of plants comprises of 1) species obtained from different geographical regions (*H. perforatum*, *J. communis*) with known active ingredients, that are already in use in pharmaceutical products and their endophytes that have already been reported to produce these metabolites; 2) species with active substances that are also used as medicine, but their endophytes were not reported as producers of host's metabolites and species with proved biological activities, but the secondary metabolites of their endophytes are completely unknown (*A. asiatica*). The mosses were selected because, despite their possible importance, the cultivatable endophytes of mosses in Hungary have not been widely examined.

6.2 Screening for host metabolite producing endophytic fungi from *H. perforatum.*

6.2.1 Identification of isolated endophytes

H. perforatum plants were collected from the Botanical Garden of the University of Szeged in autumn. The leaf, stem, root and flower parts were separated, and these parts were examined for their fungal endophyte content. Altogether 48 parts were tested involving 12-12 leaf, stem, root and flower cuttings, respectively. Then due to the intensive surface sterilization procedure a total of eight fungal strains were isolated after 7 days of incubation at 25 °C from the samples (Table 3). Three strains were isolated from the leaves and two fungi from both stems and flowers as well as one strain from the root representing the genus *Alternaria* (6), *Epicoccum* (1) and *Trichoderma* (1) (Table 3). The latest proved to be *Trichoderma harzianum*, which was confirmed after the NCBI BLAST search by the barcode identification system of this genus due to the 5 genus-specific hallmarks found in its sequence. According to the NCBI hits both the SZMC 23771 and 23772 strains were identified as members of the *Alternaria* genus (Table 3). These isolates were also investigated phylogenetically in detail due to their host metabolite production described later (6.2.2).

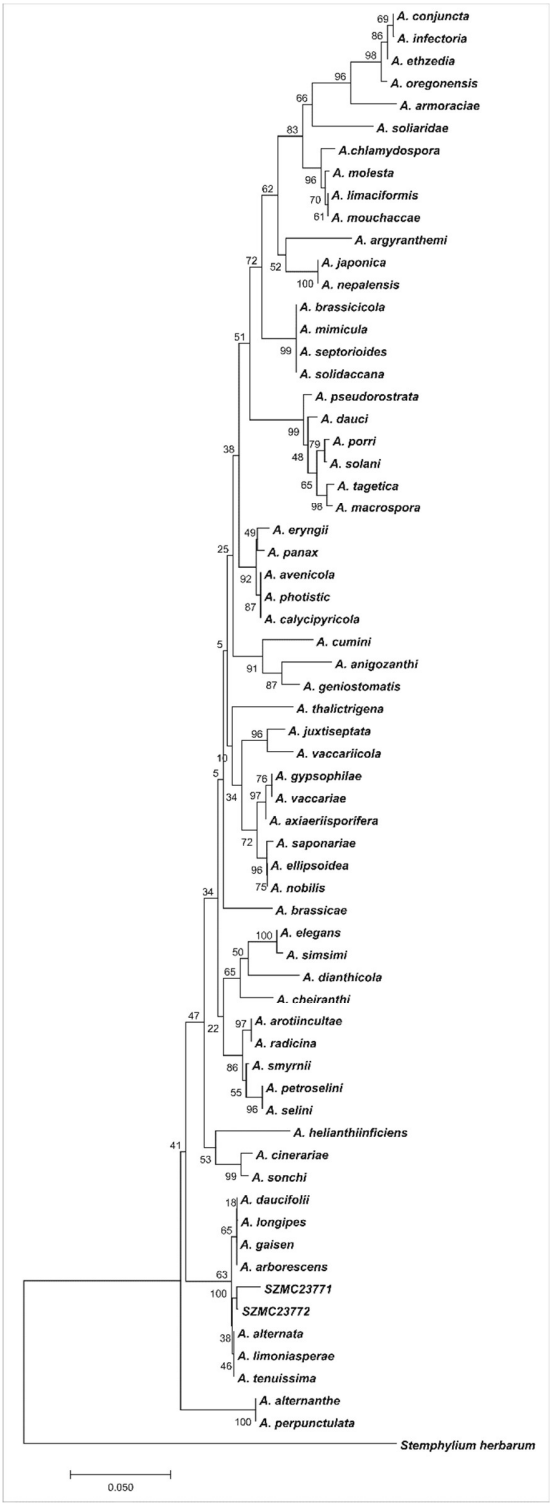

Figure 3. Phylogenetic analysis of the *Alternaria* strains proved to be the producer of emodin.

Based on the phylogenetic analysis of the ITS sequences of these two strains (Figure 3) as well as those of the ex-type and representative strains of the species available in the GenBank (Table S 15) our *Alternaria* isolates belong to the section *Alternata*.

Table 3. ***List of isolated and identified endophytic fungi from*** **H. perforatum.**

Genbank ID	**Species**	**Collection code**	**Blast hits[a]**	**Plant part**
KY613791	*Epicoccum nigrum*	SZMC 23769	510/512(99%)	Flower
KY613792	*Alternaria sp.*	SZMC 23770	536/537(99%)	Stem
KY613793	*Alternaria sp.*	SZMC 23775	499/501(99%)	Flower
KY613794	*Alternaria sp.*	SZMC 23776	521/523(99%)	Stem
KY613795	*Alternaria sp.*	SZMC 23774	491/524(94%)	Root
KY613796	*Alternaria sp.*	SZMC 23771	458/48, 96%	Leaf
KY613797	*Alternaria sp.*	SZMC 23772	520/520(100%)	Leaf.
KY613798	*Trichoderma harzianum*	SZMC 23773	551/553(99%)	Leaf.

[a]The first blast hit at 29 May 2018

The *Alternaria* isolates were identified only at the genus level due to the highly variable phylogenetic loci have found a lack of support between the earlier described phylogenetic clades and morphologically described species (Andrew et al. 2009). Numerous morphological species have been described within this genus representing same species or discrete evolutionary taxa (Armitage et al. 2015), in which eight phylogenetic lineages were identified assigning them the taxonomic rank of section (Lawrence et al. 2015). However, the commonly isolated morphologically described species as in our cases belonging mainly to the *Alternaria* genus - are

usually within the *A. alternata* species group including *A. tenuissima*, *A. arborescens*, and *A. alternata* (Andrew et al. 2009). Based on the recent classification approach of this genus, the support values (Bayesian posterior probabilities, RAxML bootstrap) of the section *Alternata* were high enough for the discrimination using the ITS sequences (Woudenberg et al. 2013). This clade involves species that are commonly referred to as small spored *Alternaria* in the literature (Lawrence et al. 2015). Members of the *Alternaria* genus were most frequently identified within the sample set based on the ITS sequences.

The fungus producing both of the examined host metabolites hypericin and emodin (6.2.2) was identified as *E. nigrum* via BLAST search of the NCBI GenBank. This species is an anamorphic ascomycete distributed worldwide colonizing different types of soils as well as host plants as an endophyte (Mims and Richardson, 2005) *E. nigrum* is considered to be a saprophytic fungus, although members of the corresponding taxon have also been described with an endophytic lifestyle (Arnold, 2007) and are isolated generally from the inner tissues of several plant species (Stuart et al. 2010).

6.2.2 Confirmation of host metabolite production of certain isolates

After the cultivation of the isolated endophytes, the ethyl acetate and chloroform-methanol extracts of both fungal mycelia and ferment broths were examined for the presence of hypericin and emodin. For the identification, HPLC-UV analysis was applied. The retention times of hypericin and emodin were 32.8 min and 16.9 min respectively.

Altogether, 32 extracts were checked for the production of both metabolites and in certain cases the observed peaks detected in the extracts fitted well to the retention time of the standard compounds (Figure 4).

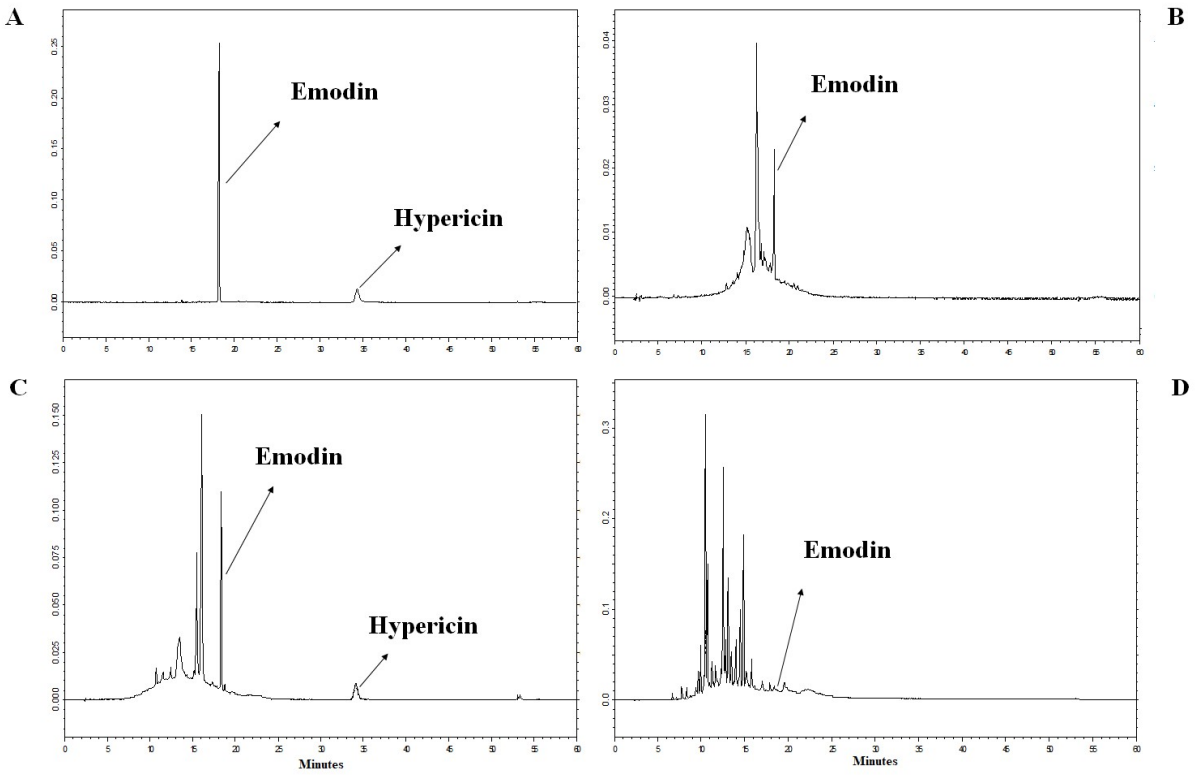

Figure 4. HPLC-UV chromatogram of the producer strains. The standard mixture of hypericin and emodin (A) as well as the mycelial extract of SZMC23771 (B), SZMC23769 (C) and SZMC23772 (D) extracted with chloroform-methanol.

It could be concluded that none of the EtOAc extracts contained the examined analytes in a measurable amount including mycelial and broth ones. However, it seemed that the chloroform-methanol extract of SZMC 23772 and SZMC 23771 mycelia contained emodin, and both hypericin and emodin was detected from the SZMC 23769 mycelial extract. It is important to consider that the host metabolites were only observed in the mycelial extracts suggesting that the compounds may be produced either intracellularly or associated to the surface of the fungal cell wall. Both strains belonging to the *Alternaria* genus (SZMC 23771 and SZMC 23772) produced emodin at similar levels, although the *E. nigrum* isolate secreted this compound more than 20 times higher quantity (over 2 µg) in broth cultured within the applied conditions. Furthermore, the yield of hypericin in the ferment broth of SZMC 23769 was approximately three quarters of emodin produced also by this strain (Table 4).

Table 4. List of the strains producing hypericin and emodin and their detected amounts in the extracts of the mycelia.

Strain number	Emodin (ng/mg)	Hypericin (ng/mg)	Emodin (ng/ml)	Hypericin (ng/ml)
	related to the mycelial weight		related to the cultivation volume	
SZMC 23771	19.9 (4.1)	BDL	87.7 (5.0)	BDL
SZMC 23772	20.8 (20.5)	BDL	71.5 (33.8)	BDL
SZMC 23769	427.9 (37.4)	320.4 (25.0)	2312.6 (19.9)	1752.0 (6.9)

BDL - below detection limit, SD values are given in brackets

The confirmation of the presence as well as the comprehensive identification of hypericin and emodin in the extracts detected by the HPLC-UV analysis was achieved by comparison with authentic reference standards using LC-HRMS and LC-HRMS/MS techniques. Suitable ionization properties were obtained in negative ESI mode for both hypericin and emodin during the MS optimization procedures, which was used later to record the high-resolution full scan ESI-MS spectra of both the standard and the fungal compounds. The retention times of the fungal hypericin and emodin were also equivalent with the standard compound as in the case of HPLC-UV measurement in all cases (**Figure 5**).

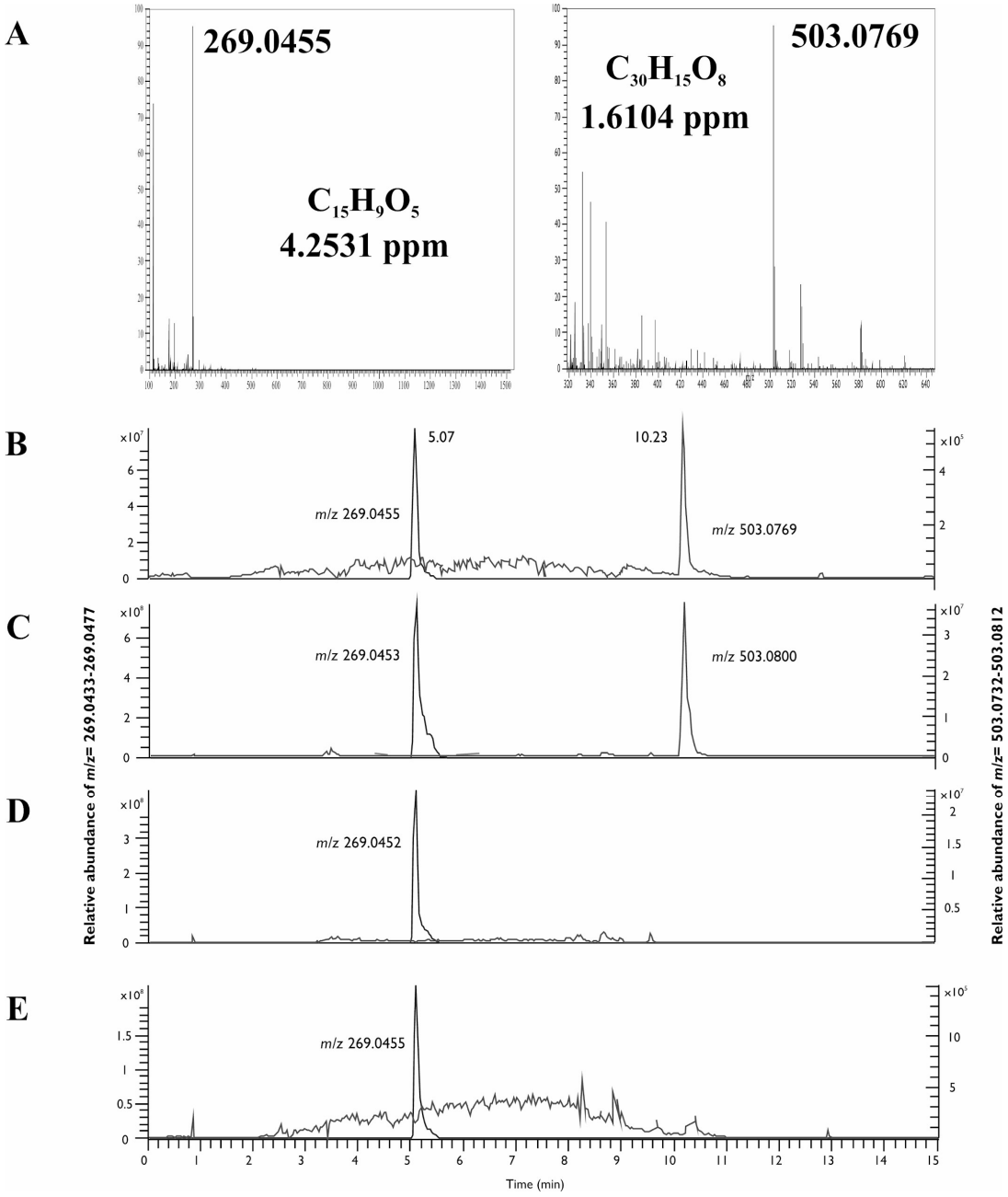

Figure 5. Full scan MS spectra of emodin ($C_{15}H_9O_5$) and hypericin ($C_{30}H_{15}O_8$) (A) and chromatograms of the standard hypericin and emodin (B), as well as the mycelial extract of SZMC 23769 (C), SZMC 23771 (D) and SZMC 23772 (E) extracted at the *m/z* values of hypericin (*m/z* 503.0732-503.0812) and emodin (*m/z* 269.0433-269.0477).

Moreover, the molecular formulas of the compounds were also served by the high mass

resolution of the applied instrument, which proved to be $C_{15}H_{10}O_5$ ([M-H]$^-$, 269.0456) for emodin in the case of each producer and $C_{30}H_{16}O_8$ ([M-H]$^-$, 503.0770) for hypericin in the case of SZMC 23769, and the full scan spectra were identical to the data obtained for the authentic standards (Figure 3). Within data dependent MS2 mode, the resulted patterns of the fragments after the collision of the above-mentioned ions as precursor ions in the HCD cell - also corresponded to the standard hypericin and emodin compounds (Figure 6 and Figure 7).

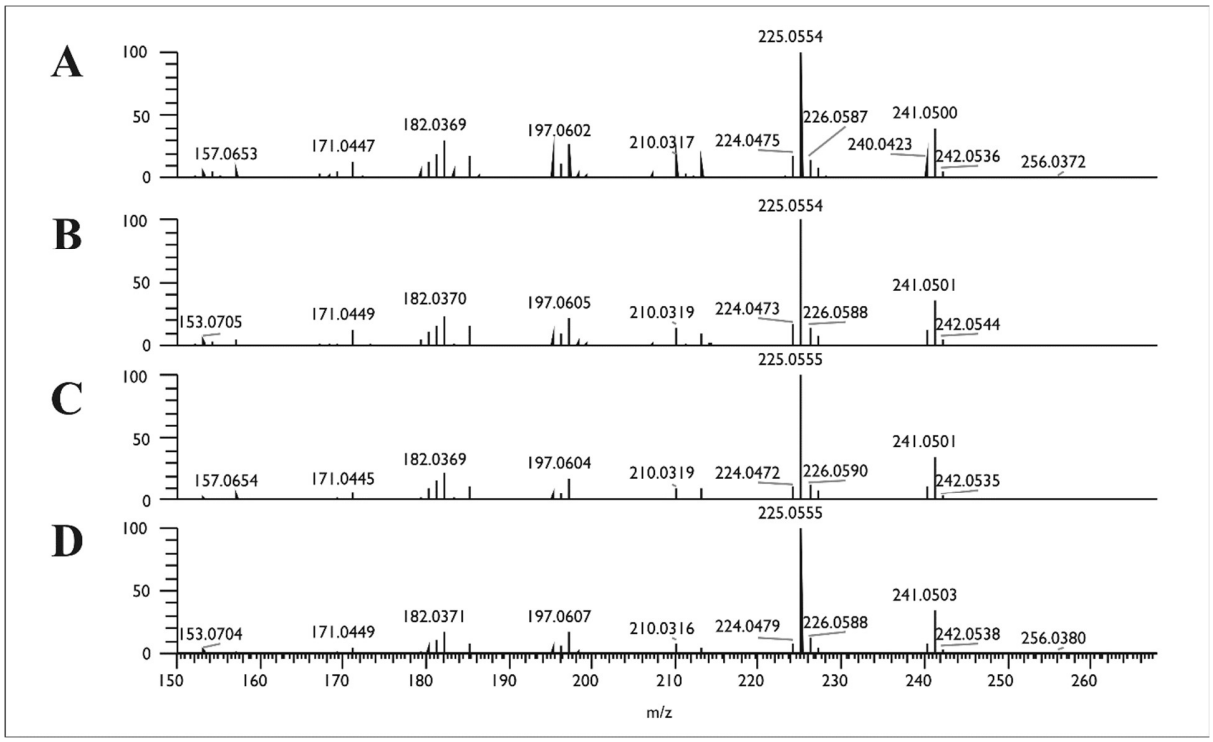

Figure 6. The MS2 spectra of emodin ($C_{15}H_9O_5$) standard (A) and the mycelial extract of SZMC 23769 (B), SZMC 23771 (C) and SZMC 23772 (D) recorded at the retention time of 5.07 min.

It was already proven that *Alternaria* species associated to plants could produce host metabolites including methyl-eugenol, capsaicin (Devari et al. 2014) and paclitaxel (Ismaiel et al. 2017), although according to our knowledge their emodin production has not been reported yet. Previously, emodin isolated from *Rhamnus triquetra* bark was found to be an efficient antifungal

toxin showing high efficiency against spore germination of 17 tested fungal species including seven species of *Alternaria* (Singh et al. 1992).

The association between plants and *Epicoccum* species also led to the production of plant metabolites by the fungi such as taxol (Somjaipeng et al. 2015) and other unique bioactive metabolites (Fatima et al. 2016) involving antimicrobial compounds such as epicorazins A–B (Baute et al. 1978), epicoccins A–D (Zhang et al. 2007), epicoccarines A–B and epipyridone (Kemami and Hertweck, 2007), flavipin (Bamford et al. 1961) and epirodins (Ikawa et al. 1978). However, our study gives the first report of their abilities to produce hypericin and emodin.

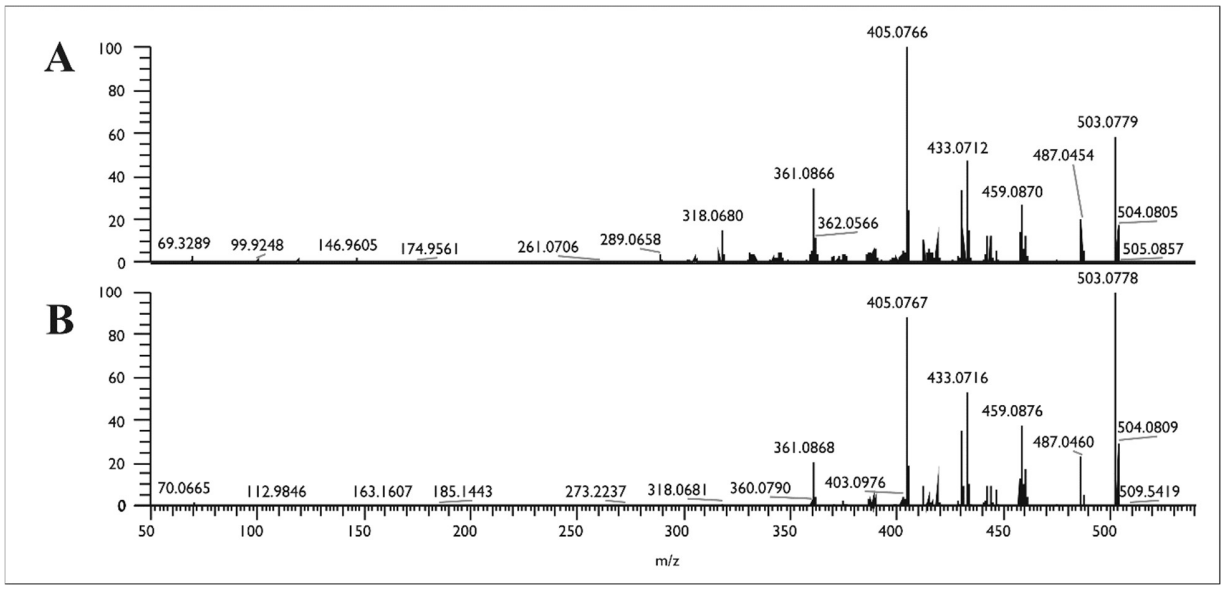

Figure 7. The MS2 spectra of hypericin ($C_{30}H_{15}O_8$) standard (A) and the mycelial extract of SZMC 23769 (B) recorded at the retention time of 10.23 min.

Previously, it has been reported that endophytic *E. nigrum* produces quinizarin, which is also an anthraquinone compound (Dzoyem et al. 2017). Furthermore, recent investigations presented the plausible explanations for being another compound, skyrin involved in the anthraquinone biosynthesis pathway of fungi (Revuru et al. 2020). Therefore, further investigations on testing the presence of this compounds in *E. nigrum* could shed some light on the actual pathway involved in the synthesis of hypericin and it will be interesting to investigate whether all producer

strains follow the same pathway, or if it is a strain specific phenomenon.

Generally, in the literature there is no available data about the amount of hypericin or emodin produced by microbes. However, for the last fungal strain isolated from *H. perforatum* producing both hypericin and emodin compounds under shake flask condition, the produced amounts were already quantitated as 0.35 ng/mg hypericin and 1.13 ng/mg emodin DW of fungal mycelia (Kusari et al. 2008). In the case of plants, the average amount of 3330 ng/mg DW of 1 and 190 ng/mg DW of emodin could be measured from *H. perforatum*, which could be reduced significantly with the application of a cold acclimation period and remained unchanged after the exposure of plants to dehydration and exogenous abscisic acid treatment (Bruňáková et al. 2015). Furthermore, the determinable amount varies between taxonomic categories (Kitanov, 2001), seasons (Southwell and Bourke, 2001) and different plant structures (Ayan and Çirak, 2008) as well as ontogenetic phases (Mártonfi et al. 2006), which could decrease the robustness of the production of these natural products. It is interesting that the amount of emodin is higher than that of hypericin in the case of fungi, while the opposite could be observed in plants.

In our study, we detected higher quantities of both hypericin and emodin produced by *E. nigrum* than the *T. subthermophila* related to the DW of the fungal mycelia, but the observed amounts of both compounds were lower than the contents reported of *H. perforatum*. Furthermore, according to the literature the hereby produced amounts were higher than what has been reported in case of other *Hypericum* species (Ayan and Çirak, 2008).

6.2.3 Antibacterial activity

The reference standards of hypericin and emodin were tested against six bacteria at the 100 µg/mL level of concentration. Both examined compounds showed moderate to high inhibitions against each bacterium in the range of 65% – 92% and 60% – 78% for hypericin and emodin, respectively (Figure 8).

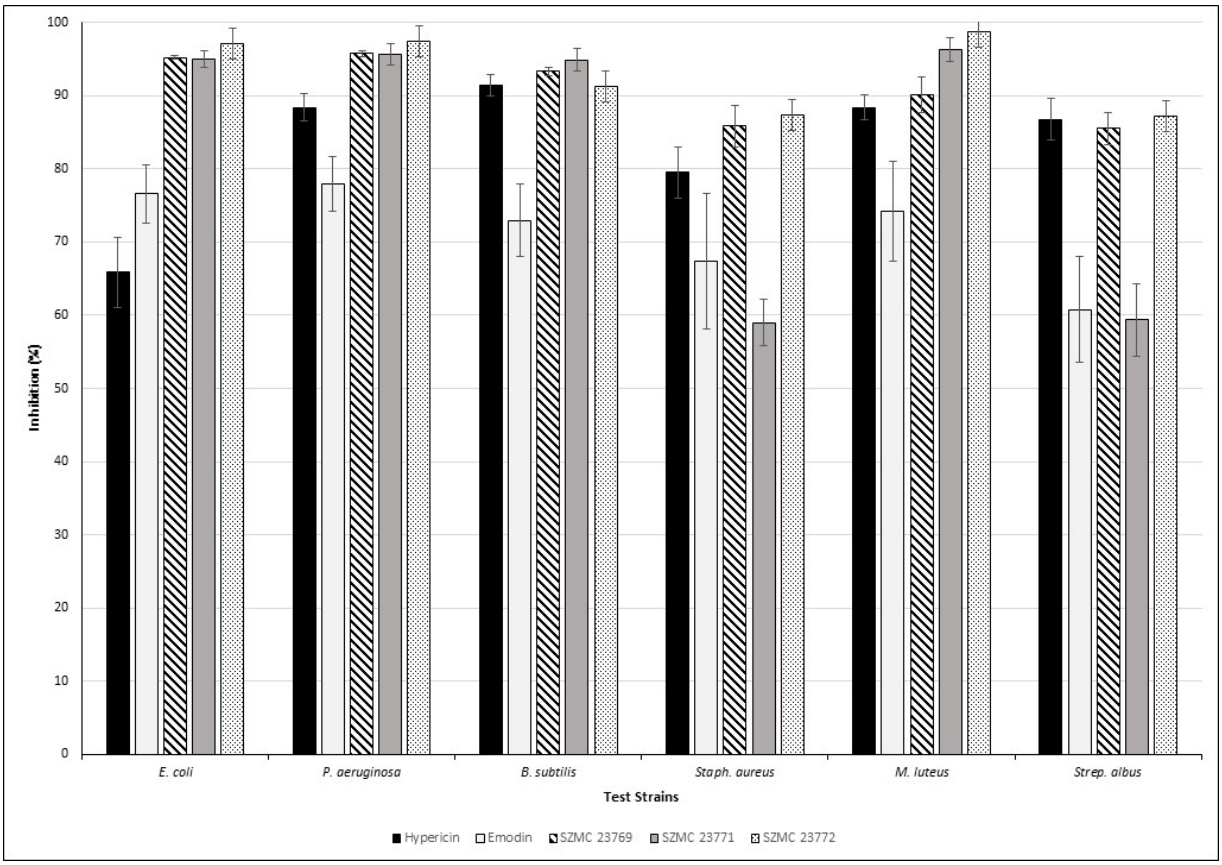

Figure 8. Antibacterial activities of the standard solutions of hypericin and emodin and the three selected fungal extracts against all test bacteria. There was a significant difference between the inhibitory values of the different extracts and the solution of both hypericin and emodin against the test bacteria ($p<0.05$).

In the case of hypericin, the highest antimicrobial activity was against *B. subtilis* and the lowest was against *E. coli*. Emodin showed the highest inhibitory activity against *P. aeruginosa* and the lowest against *Strep. albus*. It could also be concluded that the antibacterial effect of hypericin is generally higher than that of emodin except for *E. coli* (Figure 8). The antimicrobial effects of extracts of producer strains were higher than standards except the extracts of SZMC 23771 against *Staph. aureus* and *Strep. albus*. The antibacterial efficacy of emodin has been evaluated previously and proved to be exhibiting strong antibacterial activity against MRSA strains (Lee et al. 2010). The mode of inhibitory action of emodin isolated from the *Aspergillus awamori*

strain has been explained as follows: emodin induces deleterious morphological alterations such as swelling and elongation of bacterial cells and conidiation decrease and cytoplasmic retraction of fungal cells, thereby inhibiting the growth of pathogenic strains (Ismaiel et al. 2016)

6.2.4 Effect of different cultivation parameters on the host metabolite production

Two of the producer strains, SZMC 23769 and SZMC 23771 were selected to examine the dependence of host metabolite production on certain cultivation conditions including lighting and cultivation media.

6.2.4.1 Effect of dark and light conditions on the host metabolite production

Cultivation of the producer strains under dark and light conditions results in variations in the production of these compounds.

Table 5 . Production of hypericin and emodin of SZMC 23769 in dark and light conditions in terms of their mycelial DW, values of SD is given in brackets

Collection ID	Light			Dark		
	DW of mycelia (mg)	Emodin (ng/mg)	Hypericin (ng/mg)	DW of mycelia (mg)	Emodin (ng/mg)	Hypericin (ng/mg)
SZMC 23771	278.65 (21.61)	23.38 (12.76)	BDL	167.31 (14.78)	10.84 (6.91)	BDL
SZMC 23769	301.49 (18.62)	343.71 (19.65)	310.4 (25.0)	155.84 (11.94)	165.37 (20.14)	28.62 (18.23)

These results suggest that light facilitated the growth of SZMC 23769 and the production of hypericin and emodin. Although their production was lower under dark conditions, the fungi did not lose their ability to produce these metabolites. In the case of SZMC 23771, the same effect was observed, thus the amount of emodin was also lower when grown in the dark (Table 5).

In *H. perforatum*, the production of hypericin is light dependent. The metabolite is localized in the dark glands of leaves and the synthesis of hypericin takes place in presence of light. Although in case of *T. subthermophila*, the production of hypericin and emodin are light independent (Kusari et al. 2009b). On the contrary, *E. nigrum* produces a higher amount of hypericin and emodin in the presence of light than in dark related to the amount of biomass (Table 5). This suggests that the production ability and the required parameters is species specific. Considering the lower mycelial weight in the dark, it is noteworthy to mention that light is also required for the growth of *E. nigrum* SZMC 23769. A similar case was observed in *Alternaria* sp. SZMC 23771, where the biomass obtained in dark condition was considerably lower than that of mycelia obtained in illumination. Light showed a remarkable effect on the mycelial growth of *Alternaria* sp. (SZMC 23771) and the production of emodin. Previous literatures show that a 12-hour day light period is beneficial for the growth of *Alternaria*, while continuous light and dark conditions are not favourable for growth (Igbalajobi et al. 2019).

6.2.4.2 Effect of different types of cultivation medium on the host metabolite production

Various culturing conditions are often tested to optimize the production of specific compounds, such as medically important active metabolites (Zou and Hu 2017) or drug-producing microbes (Pu et al. 2013). For this purpose, the effect of cultivation medium on the host metabolite production of both SZMC 23769 and SZMC 23771 was tested using different media. For SZMC 23769, the highest yields of both hypericin and emodin were observed on PDB (Figure 9). The yield of both metabolites was moderate on MEB, while their production on CDB and on DM was substantially low. For emodin production approximately 7 times lower amount was measured on both CDB and DM than on PDB. This result supports the findings of Rabbani et al. (2011) that media conditions have varying effects on the production of fungal secondary metabolites (Rabbani et al. 2011). Similarly, in the case of SZMC 23771, the quantity of emodin was also the highest on PDB, followed by MEB/DM and CDB.

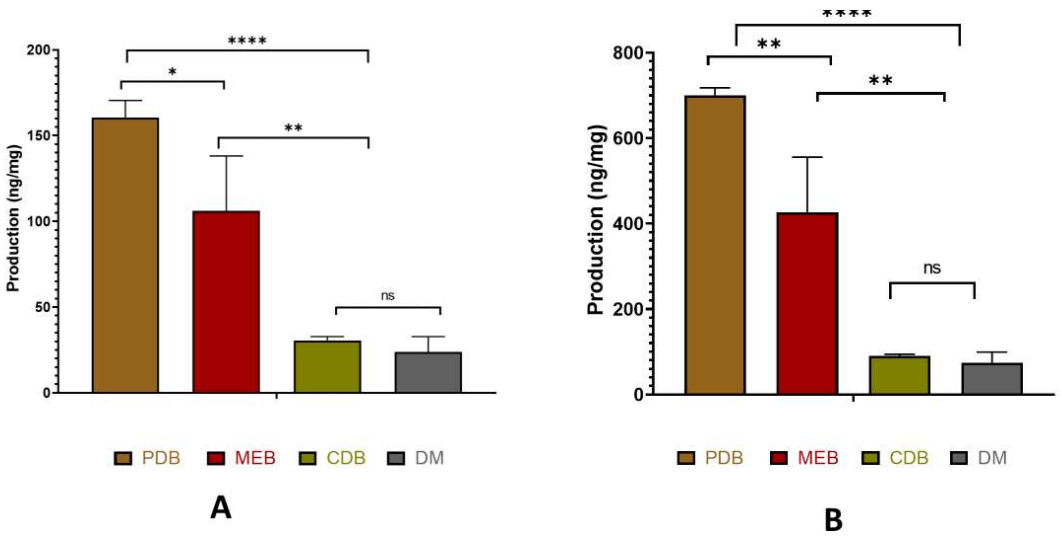

Figure 9. Hypericin (A) and emodin (B) production of SZMC 23769 in different media**.**

(P values - ****P<0.0001, ***P<0.001, **P<0.01, *P<0.05)

The media components like carbon source, nitrogen source, micronutrients significantly impact the growth and production of metabolites in fungi. Therefore, optimization of culturing conditions using different growth media is necessary to increase the production of a compound of interest (VanderMolen et al. 2013). PDB contains potato starch, which supports growth and pigment production in many filamentous fungi. Previous results also support that naphthoquinone production is also higher in PDB (Kaur et al. 2015). When complex nitrogen sources are used such as peptone and yeast extract, it stimulates pigment formation (Carels and Shepherd, 1977). The presence of inorganic nitrogen sources also lowers the production of pigments (Kaur et al. 2015). These might be the reason why in CDB and DM fungi produced both emodin and hypericin in low quantities MEB and PDB contain lots of organic nutrients such as malt extract, peptone and starch, all of which influence gene expression regulation and may activate the respective metabolic pathways (Pradeep et al. 2013).

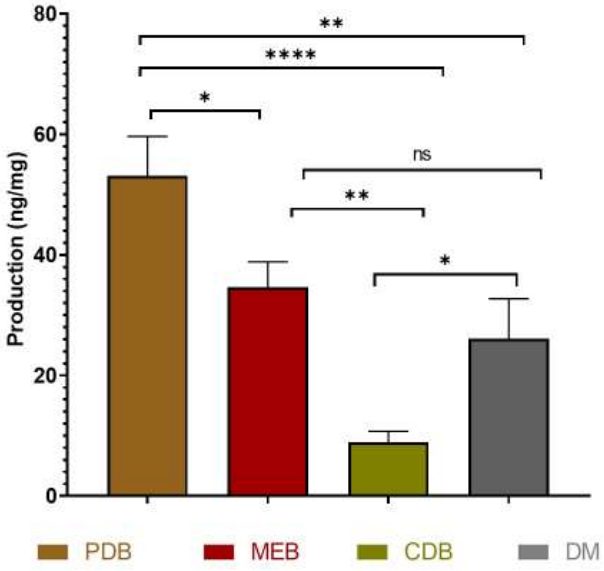

Figure 10. Emodin production of SZMC 23771 in different media.

(P values - ****P<0.0001, ***P<0.001, **P<0.01, *P<0.05)

The presence of organic nitrogen source is essential for optimal growth and metabolite production (Carels and Shepherd, 1977). These results suggest that PDB would be the most suitable media to produce hypericin and emodin by SZMC 23769 and emodin by SZMC 23771 in larger quantities in the future (Figure 9, Figure 10).

6.2.5 Attenuation of host metabolite production during sub-cultivations

The production of a bioactive compound by an EF can be stimulated in the host plant or by a host plant extract. When grown *in vitro*, an endophyte may continue to produce a bioactive material, or this may cease after a certain time (Kusari et al. 2012). Therefore, in certain cases, additional examinations are needed to discover what factors could stimulate endophytes to continue host metabolite synthesis *in vitro* (Owen and Hundley, 2004). To investigate whether host metabolite production either persists or ceases during repeated sub-cultivations, a detailed study of metabolite production was undertaken over several generations in four different media. In shake-flask fermentation of the producer strains (SZMC 23769 and SZMC 23771), a clear decrease in the

production of both host metabolites was observed from the third to the tenth-generation subculture (Figure 11, Figure 12).

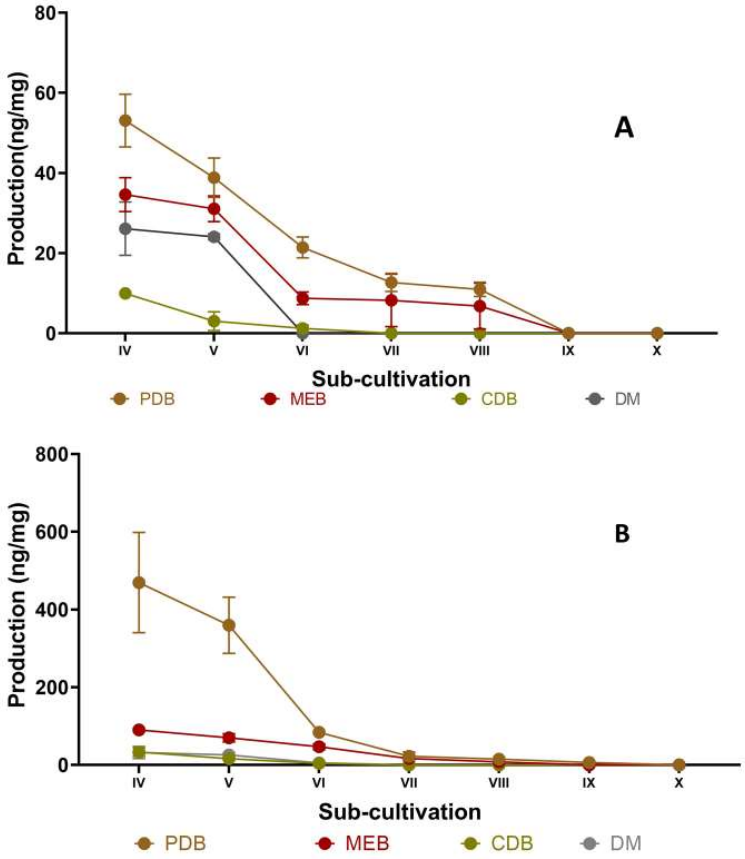

Figure 11. Host metabolite production of SZMC 23769 during Sub-cultivations: (A) hypericin production (B) emodin production.

In the case of SZMC 23769 the hypericin production ceased in the ninth generation in PDB and MEB and the production of emodin ceased in the tenth generation in PDB and IXth generation in MEB, (Figure 11) but the production ability stopped two generations earlier in the other two mediums. The amount of emodin ceased also completely from the tenth generation in SZMC 23771 (Figure 12). One of the major limitations in bioprospecting of EF is the problem of attenuation during sub-cultivation (Ansari and Butt, 2011) and we observed a similar challenge regarding hypericin and emodin production. These gradual losses in the production ability of host metabolites during subsequent generation suggests that the expression of the background genes is decreased in

the isolates during the sub-cultivations. This phenomenon has also been reported in case of camptothecin production by *Fusarium solani*, where its production gradually decreased during sub-cultivations (Kusari et al. 2009a). Another study also showed the reduction of host plant derived compound production in an endophytic *Aspergillus flavus* over 11 generations (El-Hawary et al. 2020). Similarly, in other cases, the sustainable production of camptothecin and Taxol in EF up to 10 generations were observed (Ma et al. 2011) It is presumable that the endophytic fungus might have acquired BGCs from the plant either by co-evolution or LGT initially and in the absence of host plants the acquired genes might get silenced due to the lack of host stimuli (Kusari et al. 2009a; El-Hawary et al. 2020). Various factors could be responsible for the attenuation process in hypericin production. It might be due to the difference in environmental factors outside the host (Shwab and Keller, 2008), Absence of cross activation signals from the plants or biosynthetic precursors within the plant or the presence of coexisting endophytes (Jamwal and Gandhi, 2019). Due to the lack of information about the host selection and interaction of the endophytes, it is impossible to elucidate the exact mechanism of attenuation (Jamwal and Gandhi, 2019). Kusari et al. (2009b) proposed that the biosynthetic pathway of hypericin and emodin in fungi is different from that of plants, and based on our results it seems that the presence of the plant partner is needed to activate the specific

gene clusters in our isolates for persistent metabolite production.

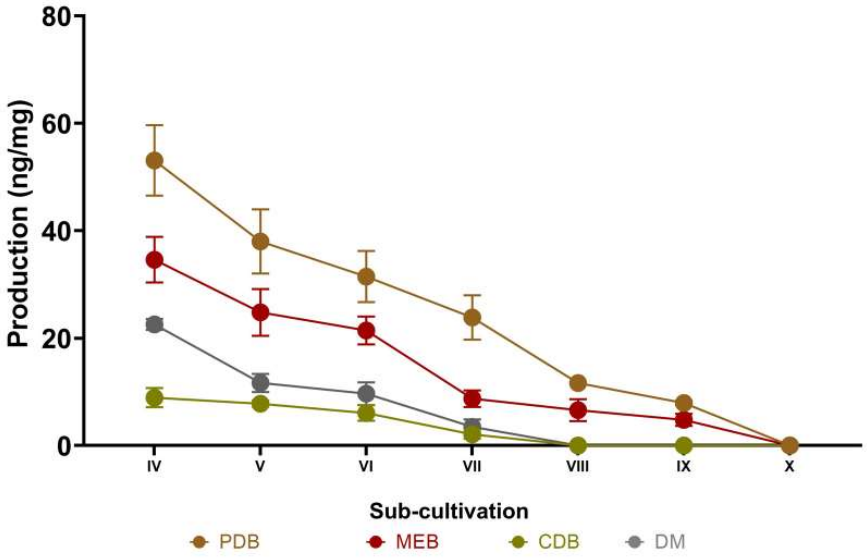

Figure 12. Emodin production of SZMC 23771 during sub-cultivations.

The exact mechanism of why fungi produce host metabolites is still not experimentally proved yet. It is arguable, whether the fungus acquired the specific gene clusters through coevolution, if yes then it also raises the question why members of a diverse group of fungi present in the same plant produce the same compound. For example, 19 different fungal genera are found to be producing Taxol (Mousa and Raizada, 2013). If endophytes are considering as an alternative source for the production of these metabolites, further research is required to unravel this mechanism.

6.2.6 Effect of different elicitors on the attenuated strains

As the biosynthesis of certain compounds outside the host is difficult for EF, elicitation is proved to be an effective strategy to induce the secondary metabolism. This approach has been predominantly used in microbial systems. Elicitors are signalling molecules, which induce the synthesis of secondary metabolites during the fermentation process (Venugopalan and Srivastava, 2015, Zhao et al. 2010). Compounds like serine and silver nitrate were used to enhance Taxol biosynthesis in *Nodulisporium sylviforme* (Zhao et al. 2011), and salicyclic acid was used to induce

camptothecin production in *Trichoderma atroviride* (Pu et al. 2013).

To restore the production of hypericin in SZMC 23769, the fermentation medium was supplemented with different kinds of elicitors (Table 6). Our results suggest that the ferment broth of the producer strains did not have any positive impact on the production of hypericin and emodin in attenuated strains. This proves that the spent broth does not contain any element that can stimulate the biosynthetic pathway of hypericin or emodin. However, when emodin was added in the fermentation medium in two different concentrations as an elicitor, small quantities of hypericin was detected in the mycelial extract, however there were no traces of emodin in the ferment broth extract.

Table 6. Effect of different elicitors in production of hypericin in attenuated strain of SZMC 23769.

Elicitors	**Experimental setup**	**Effect on the production (ng/mg)**	
		Hypericin	**Emodin**
Tea solution of *H. perforatum*	1:1 solution of tea and PDB as a growth medium	BDL	BDL[a]
	1.2 g of PDB dissolved in 50 mL of tea as a growth medium	8 .812 ng/mg	BDL
Fresh tissues of leaves and stems of *H. perforatum*	0.1 g/L of crushed stem and leaves supplemented in PDB	10.24 ng/mg	BDL
Emodin addition	50 µg/mL	54.90 ng/mg	BDL
	100 µg/mL	95.93 ng/mg	BDL
Ferment broth of SZMC 23769 producer strain	1:50 supplementation in PDB	BDL	BDL
	2:50 supplementation	BDL	BDL

[a]BDL: Below Detection Limit

The effect of tea solution of *H. perforatum* were also tested in two concentrations, where

the applied higher tea amount could restore the production of hypericin in low amount, but no traces of emodin were observed (Table 6) This suggests that the fresh and dried plants might have provided certain elicitors that stimulated the biosynthetic pathway, however detailed investigation is needed to elucidate the exact mechanism. Previously, it has been illustrated in the case of EF producing camptothecin that the reason of attenuation is due to the absence of the host plant enzyme, strictosidine synthase (Kusari et al. 2011). Hence, the addition of the host plants will be one of the solutions to re-activate the biosynthetic mechanism of this fungus in axenic culture outside the host.

6.3 Investigation of endophytic fungi isolated from *J. communis*, *A. asiatica* and several mosses.

Altogether 240 parts were tested involving 60 cuttings of leaf, stem, root and cone from 12 different plant samples of *J. communis*. For *A. asiatica*, a total of 126 segments (Leaf-63, Stem-63) were examined for the presence of EF from 21 different plants, while for mosses, the whole plant of 40 different species were used and one plant was considered as one segment for endophytic isolation.

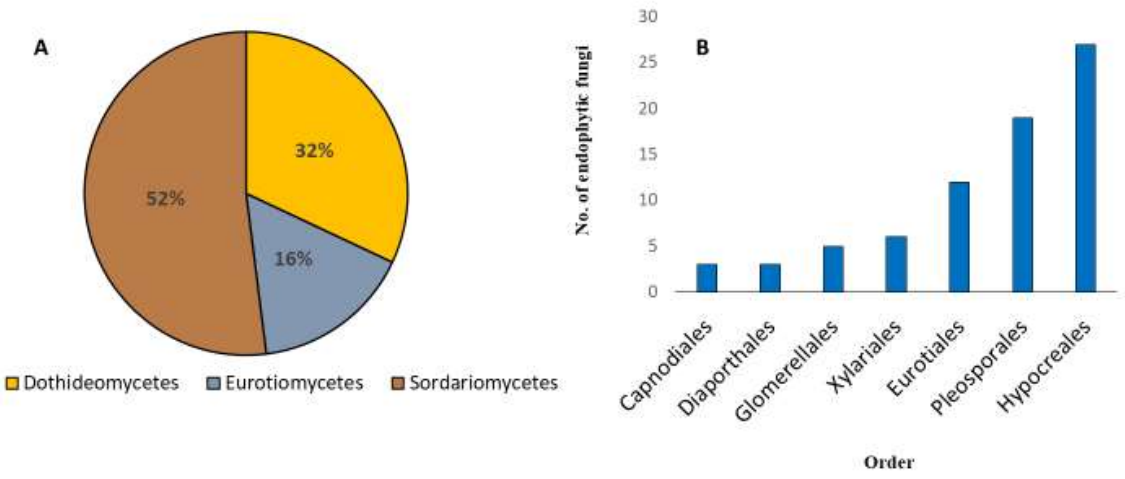

Figure 13. Distribution of EF isolated from *J. communis* into classes (A) and orders (B).

6.3.1 Investigation of fungal endophytes isolated from *J. communis*

6.3.1.1 Biodiversity of endophytic fungi isolated from *J. communis*

Altogether 75 EF were isolated from *J. communis* distributed into 3 main classes and 8 main orders (Figure 13). The predominant class was found to be Sordariomycetes, which were similar to the previous studies in *Juniperus* endophytes (Kusari et al. 2009a). Most of the isolates belonged to Hypocreales, and the rest of the isolates were members of the taxa Pleosporales and Eurotiales.

6.3.1.2 Isolation rate and fungal richness, host and tissue specificity of fungi isolated from *J. communis*

To characterize the biodiversity of *A. asiatica* EF, the Shannon diversity index (*H'*) Simpson's Dominance (*D*), and Margalef's richness (*D mg*) have been calculated The Shannon-index revealed higher certainty of endophytic fungal species consistency in the stem compared to that of the other parts in *J. communis.* Moreover, the Simpson's-index clearly showed that the stem harbored highly diverse fungal endophytes compared to those harbored by other parts. Finally, based on Margalef's-index the stems have high taxonomic richness and cone had the lowest compared to the other tissues in *J. communis* (Table 7).

Table 7. Biodiversity parameters of EF isolated from *J. communis*.

Diversity index	Stem	Root	Leaf	Cone	Total
Simpson's Dominance (D)	0.912	0.775	0.788	0.666	0.92
Shannon (H')	2.582	1.630	1.950	1.214	2.85
Pielou's evenness (J)	0.931	0.910	0.847	0.48	0.89
Margeref richness	4.218	1.894	3.176	1.365	5.32

The stems of *J. communis* harbored 11 unique fungi, whereas 4 and 2 were found in leaf and cone (Figure 14). Interestingly, the roots of *J. communi*s did not harbor any unique fungi. This shows that some species seem to be tissue specific. *Xylaria* species were found only in cone, while *Pestalitiopsis* and *Bipolaris* were found only in leaf, whereas *Curvularia*, *Aspergillus*, *Didymella*

and *Purpureocillium* species were specifically found in stems. The biodiversity parameters revealed higher diversity of endophytic fungal species in the stem compared to that of the other parts in *J. communis* (Figure 15). *Fusarium* strains were more abundant in roots than in other tissues.

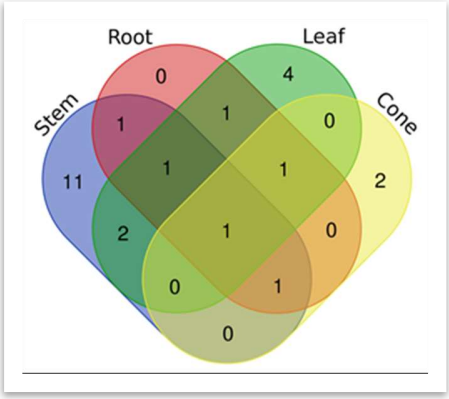

Figure 14. Venn diagram showing the common and unique fungi along the tissues of *J. communis*.

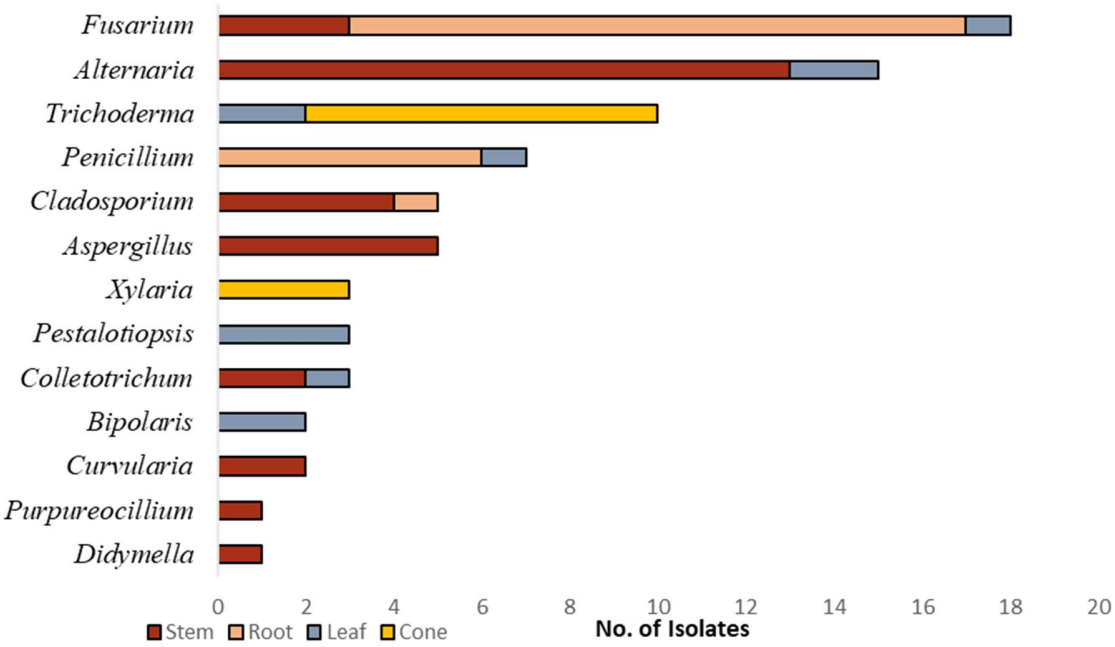

Figure 15. Distribution of EF of *J. communis* at genus level.

6.3.1.3 Antimicrobial effects of fungal extracts of *J. communis* endophytes

Gram-positive bacteria were found to be more susceptible against the extracted endophytic metabolites than Gram-negative bacteria due to the higher number of highly active (>90%) extracts (Figure 16, Table S 2, Table S 3, Table S 4, Table S 5). For *B. subtilis*, the highest number of highly active extract were recorded from the EtOAc extracts of ferment broth (55), while the lowest amount of effective extracts (22) was obtained from the hexane based solvent partitions. Against *E. coli* the mycelial and chloroform extracts proved to be the most effective.

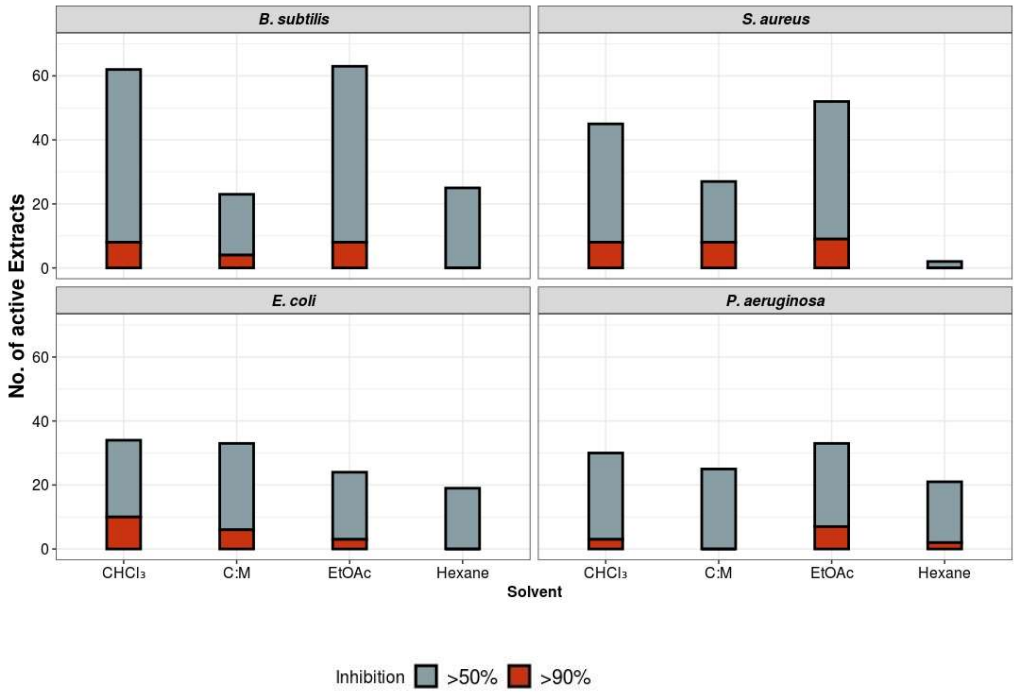

Figure 16. Summary of the antibacterial effects of endophytic extracts isolated from *J. communis* (C:M - chloroform: MeOH (4:1) extract of mycelia)

In the case of *S. aureus,* the highest number of effective extracts were obtained from the EtOAc extracts (43) followed by chloroform partitioned ferment broth samples (37). It is important to highlight that the SZMC 27155 was highly active against all bacteria, but it was not active against the tested yeast and plant pathogens. The EtOAc, $CHCl_3$ extracts of SZMC 27164 and SZMC 27031 isolates showed remarkable inhibitory effects against all tested bacteria and the

mycelial extracts of these isolates were also active against phytopathogens and yeasts. The *Trichoderma* isolates of this plant showed activity at least against one test microbe. The extracts of SZMC 27205 strain showed significant inhibitory activity against both Gram-positive and Gram-negative bacteria. With respect to taxa, *Fusarium, Pestalotiopsis, Trichoderma, A. fumigatus* and *Purpureocillium lilacinum* strains showed significantly high bioactivity and will be suitable for further investigations.

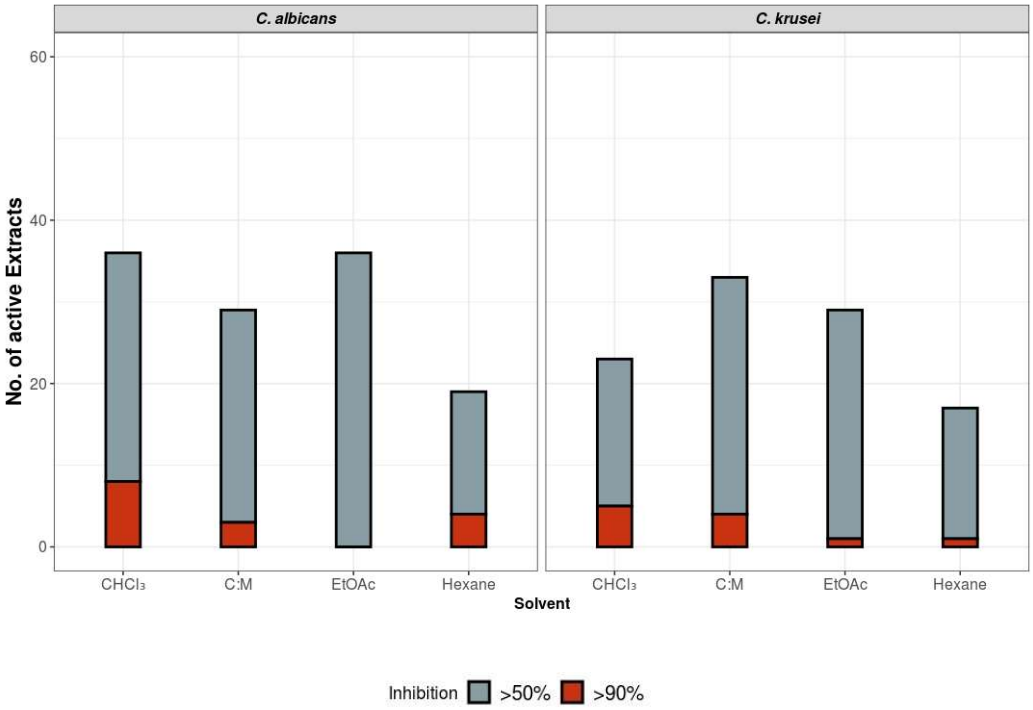

Figure 17. Summary of the antifungal effects of endophytic extracts isolated from *J. communis* (C:M - chloroform: MeOH (4:1) extract of mycelia).

Altogether, 27 extracts showed inhibitory effects against yeasts, which is over 90% (Figure 17). Interestingly, both chloroform and mycelial extracts of the ferment broth inhibited *C. albicans,* while *C. krusei* was mainly susceptible to the EtOAc and mycelial extracts (Table S 2, Table S 3, Table S 4).

Previous works showed that the EF of *J. communis* were excellent sources of antimicrobial

compounds (Elhariry and Gherbawy, 2014). In our study at least one solvent partition of 58 isolates were active against *B. subtilis, S. aureus* and *C. albicans*. However, only a few extracts, particularly the mycelial extracts were found to be active against the tested phytopathogens, Specifically mycelial extracts of *Trichoderma* and *Purp. lilacinum* were active against both of the tested fungi. *F. culmorum* was found to be more resistant than *R. solani* (**Table S 14**).

6.3.2 Investigation of fungal endophytes isolated from *A. asiatica*

6.3.2.1 Biodiversity of endophytic fungi isolated from *A. asiatica*

Altogether, 83 EF isolated from *A. asiatica* (Figure 18). The EF were distributed into 3 classes and 5 orders, where the members of Sordariomycetes were the most abundant.

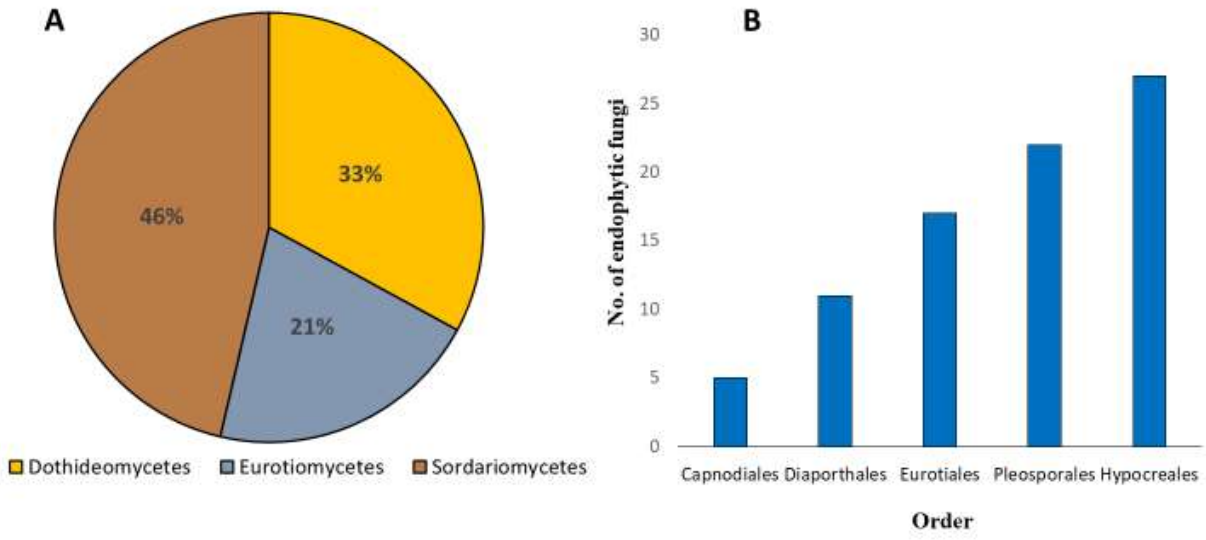

Figure 18. Distribution of EF isolated from *A. asiatica* into classes (A) and orders (B).

6.3.2.2 Isolation rate and fungal richness, host and tissue specificity of fungi isolated from *A. asiatica*

There was no significant difference between the diversity index of J. communis and *A.asiatica*, although, the sampling tissue segments were different (Table 8). The IR was recorded as 0.75 and the fungal richness of EF was 17.

Table 8. Biodiversity parameters of EF isolated from *A. asiatica*.

Diversity index	**Stem**	**Leaves**	**Total**
Simpson's Dominance (D)	0.9	0.87	0.93
Shannon (H')	2.62	2.36	2.96
Pielou's evenness (J)	0.89	0.87	0.9
Margeref richness	4.72	3.82	5.86

Although the number of fungi in the stem was higher than leaves in case of *A. asiatica*, the notable difference was comparatively low (Figure 19).

The number of fungi in the stem was higher than leaves, but this difference was comparatively low. *Curvularia*, *Phomopsis* and *Simplicillium* species were found only in leaves, while *Aspergillus*, *Trichoderma* and *Stemphylium* species were isolated only from the stem. (Figure 19, Table S 1). Therefore, these species could be even tissue specific in *A. asiatica*, but to clarify this statement larger sample set would be favorable. It should also be considered that the host specificity of EF can change the prevalence of their taxa in a particular plant and the divergence in the EF community might be harbored in specific host tissues due to the histological difference and nutritional availability (Arnold et al. 2007).

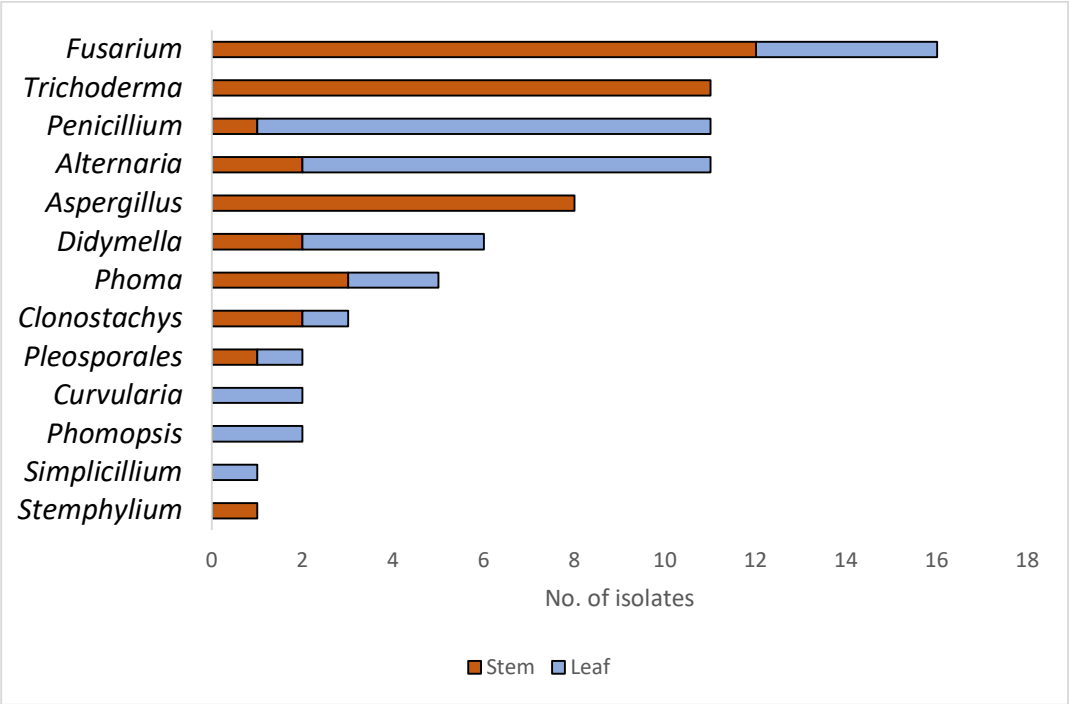

Figure 19. Distribution of EF isolated from *A. asiatica* at genus level.

6.3.2.3 Antimicrobial effects of fungal extracts of *A. asiatica* endophytes

Altogether, 328 extracts were tested against both four bacteria and two yeasts and two phytopathogenic fungi (Table S 6, Table S 7, Table S 8, Table S 9, Table S 14). Our results revealed that altogether 54 hexane-, 78 EtOAc-,73 $CHCl_3$- and 78 mycelial extracts were active against at least one test strains. Remarkable high number of extracts (53) were active against *B. subtilis*, and 50% of the extracts were active against *S. aureus* (Figure 20). But low percentage of extracts were active against Gram-negative bacteria including *E. coli* (31%) and *P. aeruginosa* (28%). *D. glomerata* (SZMC 27102) exhibited higher activity against all of the tested microbes the SZMC 27125 and SZMC 27126 strains showed a remarkable activity against Gram-positive bacteria and the mycelial extract of these EF showed high activity against Gram-negative bacteria, but they did not show any activity against yeasts and phytopathogens. Most of the extracts of *Fusarium* species exhibited remarkable antimicrobial activities against yeasts, but none of them were active against the two phytopathogen isolates (Table S10). The EtOAc extracts of *Aspergillus* isolates (SZMC 27077, SZMC 27078) showed a significant activity (>90%) against *B. subtilis, S. aureus, P.*

aeruginosa and *C. albicans*.

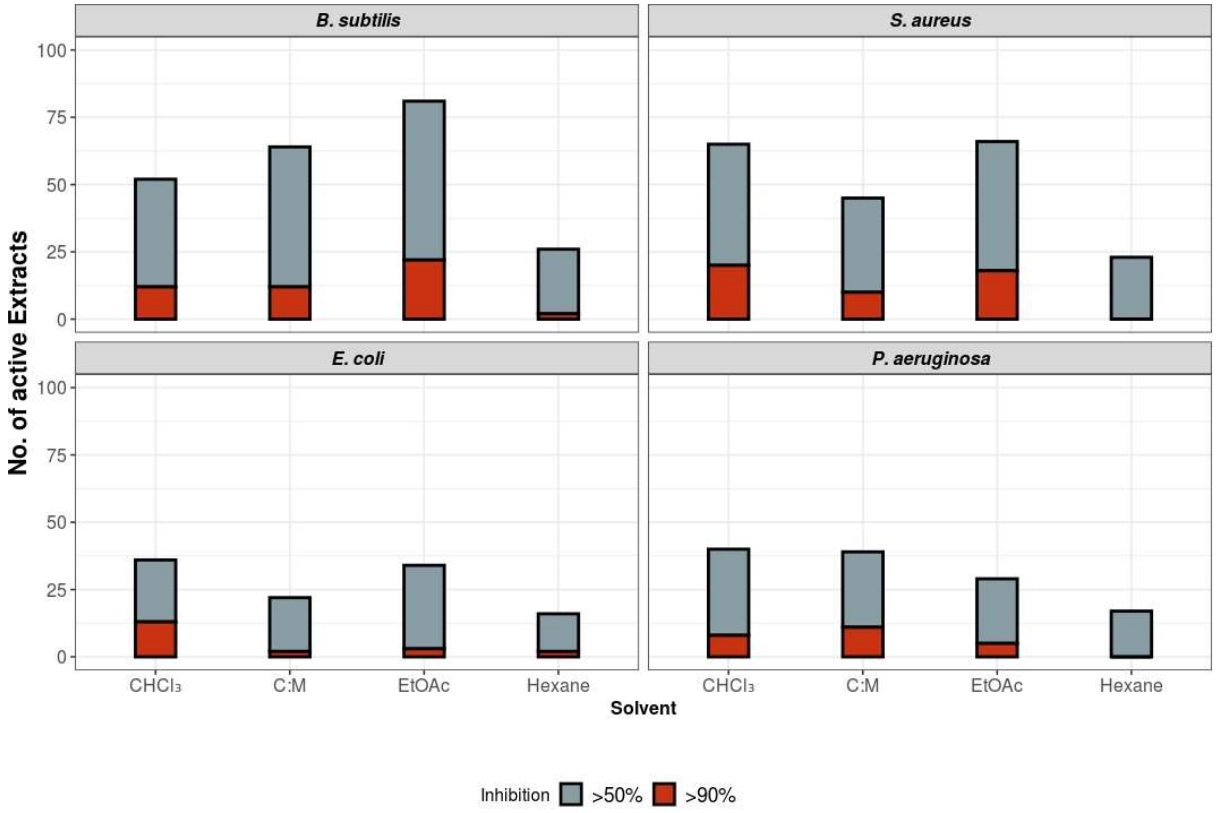

Figure 20. Summary of antibacterial effects of endophytic extracts isolated from *A. asiatica* (C:M - Chloroform: MeOH (4:1) extract of mycelia).

During the antifungal activity testing, *C. krusei* was found to be more resistant against the extracts than *C. albicans* (Table S 6, Table S 7, Table S 8, Table S 9). In total 46 strains were found to be possessing more than 90% inhibition against at least one test pathogen (Figure 21). Taxa wise, *Aspergillus*, *Penicillium*, *Fusarium* were found to have metabolites with effective antifungal activity. Moreover, similarly to the EF of *J. communis*, chloroform and mycelial extracts of *Trichoderma* species were active against *R. solani* and *F. culmorum*

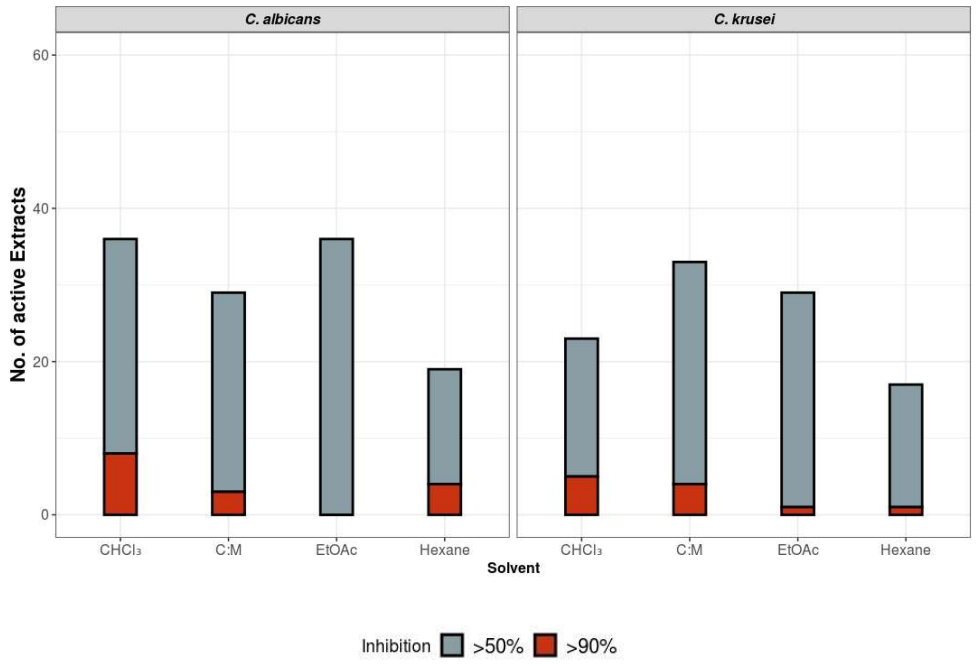

Figure 21. Summary of antifungal effects of endophytic extracts isolated from *A. asiatica* (C:M - chloroform: MeOH (4:1) extract of mycelia).

6.3.3 Investigation of fungal endophytes isolated from mosses

6.3.3.1 Biodiversity of endophytic fungi isolated from mosses

To date, most of the studies are focused on the endophytic community of seed plants to completely understand the dynamics of endophytic biodiversity, investigating different clades of plants is necessary. This study was undertaken to investigate the biodiversity of EF also in mosses.

Altogether, 40 EF were isolated from 126 plant segments of 42 different mosses, which is distributed into 3 classes and 7 orders. Similarly, to *J. communis* and *A. asiatica*, Sordariomycetes was the predominant class followed by classes of Dothideomycetes and Eurotiomycetes, while the dominant order was Hypocreales (Figure 22). The dominant taxa found in mosses were *Trichoderma* and *Alternaria* (Figure 22).

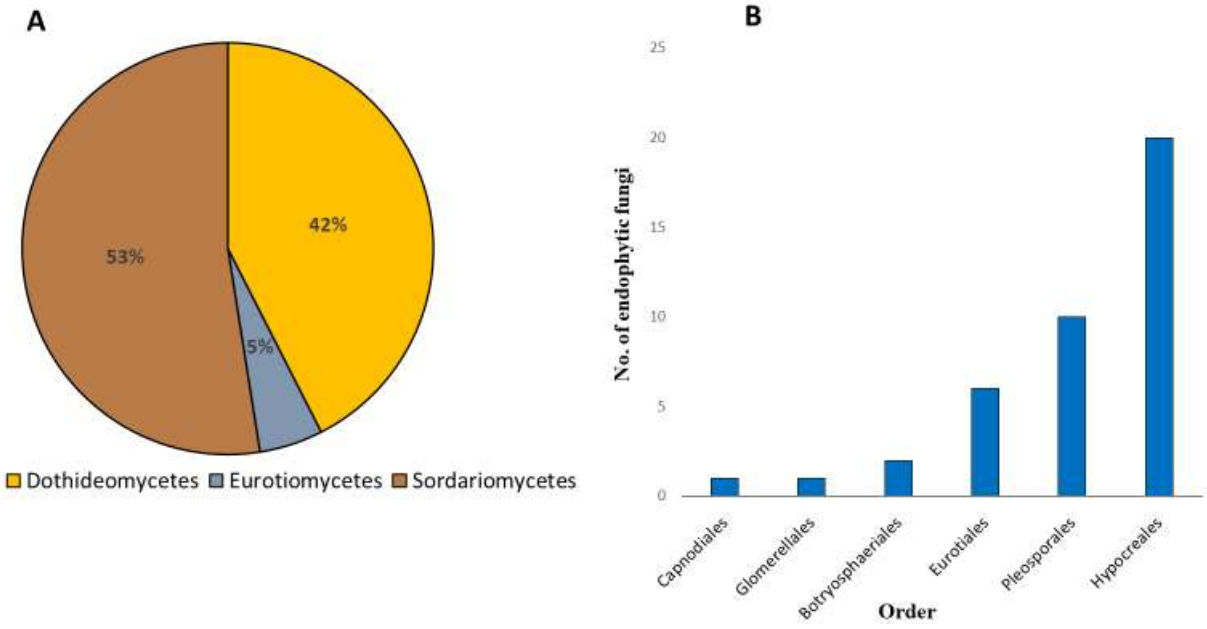

Figure 22. Distribution of EF isolated from mosses into classes (A) and orders (B).

Besides the dominant *Trichoderma* and *Alternaria* genera, the *Aspergillus, Phoma* and *Fusarium* genera were also presented. The presence of *Dothiorella gregaria* (SZMC 27238 and SZMC 27239) as moss endophyte was only observed in this study. Two isolated species were identified only at the order level as Pleosporales.

6.3.3.2 Isolation rate and fungal richness, host and tissue specificity of fungi isolated from mosses

The IR of mosses was 0.37. Such low IR was previously reported in isolation from the Antarctic region (Bradner et al. 2000; Tosi et al. 2002). Totally, 40 EF were isolated and the fungal richness was calculated to be 10. The genera isolated from mosses were different compared to the previous studies (Bradner et al. 2000; Tosi et al. 2002). This implies that the diversity of EF also differs based on the geographical region. Shannon index shows that the diversity index is moderate despite of the low IR (**Table 9**)

Table 9. Biodiversity parameters of EF isolated from mosses.

Diversity index	Parameter value
Simpson's Dominance (D)	0.85
Shannon (H')	2.43
Pielou's evenness (J)	0.82
Margeref richness	4.67

The comparison of biodiversity indexes of all three plants shows that the fungal endophytes isolated from *A. asiatica* and *J. communis* are highly diverse compared to mosses (Table 7,

Table **8**,Table 9) The overall diversity of the fungal endophyte population inhabiting three plant species, represented by Shannon index H′ were 2.96, 2.85, 2,43 for *A. asiatica, J. communis*, and mosses respectively. This shows that the species richness and evenness is lower in moss samples than in the other two plants. The relative diversity (J) also reveals that *A. asiatica* had the highest 'J' value of 0.90, followed by *J. communis* and mosses with a 'J' value of 0.89 and 0.82, respectively. The results clearly corroborate that mosses harbour the least diverse endophytic community comparing to other two plants.

6.3.3.3 Antimicrobial effects of fungal extracts of moss endophytes

Totally, 160 extracts (120 broth and 40 mycelial) were tested against four bacteria and two yeasts (Table S 10, Table S 11, Table S 12, Table S 13). Our results showed that 136/160 (85%) of the extracts showed inhibitory activity against at least one test bacterium. Among 40 EF, almost 50% were bioactive against at least one bacterium (Figure 23). 54 % of the EtOAc extracts showed inhibition against Gram-negative bacteria, which was 52% in the case of mycelial extracts. Similarly, to the EF of the other two plants, hexane extracts of moss isolates in certain cases showed inhibitory activities (Figure 23).

It can be highlighted that *Trichoderma* isolates were found to be active against most of the tested pathogens, including *C. albicans*.

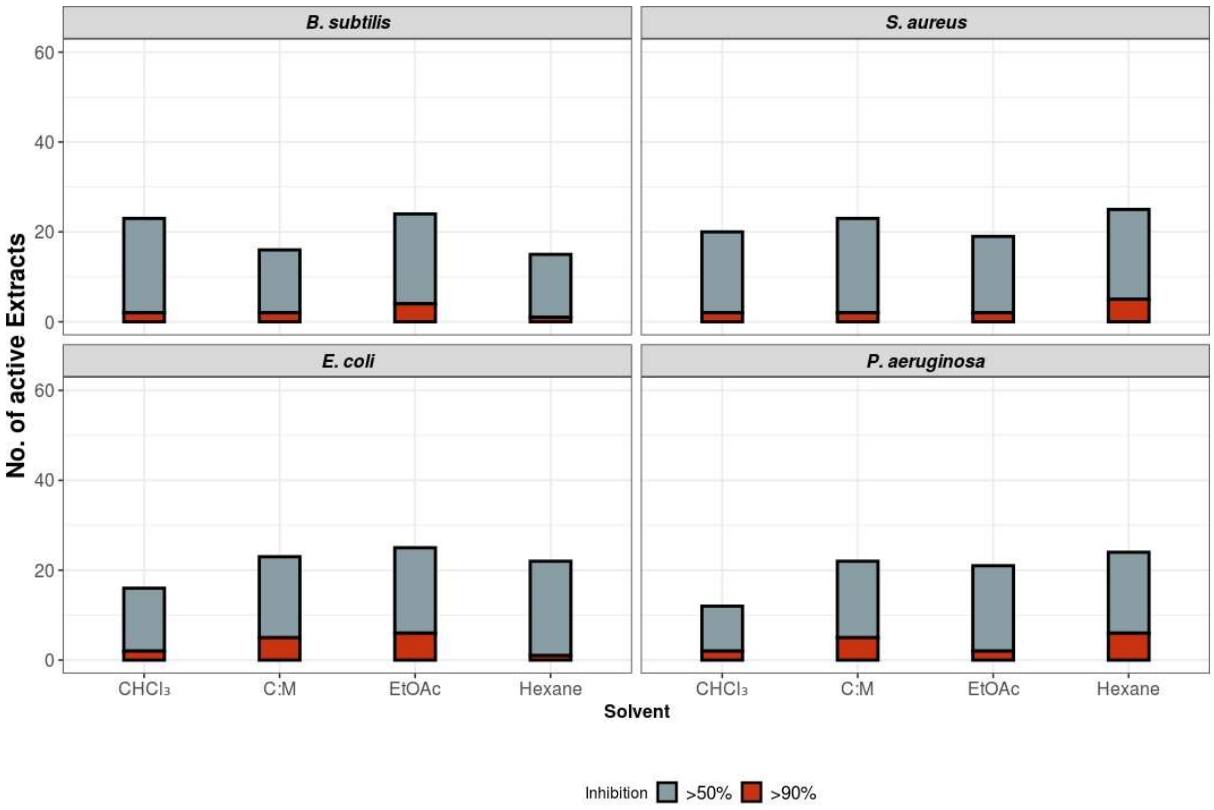

Figure 23. Summary of antibacterial effects of endophytic extracts isolated from mosses (C:M - chloroform: MeOH (4:1) extract of mycelia).

None of the extracts exhibited > 90% inhibitions against *C. albicans*, while a few EtOAc extracts exhibited >90% activity against *C. krusei*. None of the Previous studies reported about antibacterial activity of moss endophytic bacteria (Lan et al. 2020). But this is the first report regarding the bioactive effects of EF from mosses. There were no significant differences in the number of active extracts partitioned with solvents. The metabolites of the SZMC 27257 strain were found to be active against all of the tested bacteria and the metabolites of *Alternaria* SZMC 27228 strain presented >90% inhibitory activity against *B. subtilis* and *S. aureus*. However, only three EtOAc extracts showed >90% inhibition against *C. krusei* and none of the extracts were showing remarkable activity against *C. albicans.* Comparing to the other two hosts, mosses harboured fewer bioactive EF against bacteria and yeasts.

Interestingly the mycelial extracts of 20 isolates inhibited the growth of the plant pathogen

R. solani (Table S 14). Regarding the inhibition of plant pathogens, similarly to our results, it was reported that endophytic bacteria from mosses are active against plant pathogenic bacteria and also promote the plant's growth (Shcherbakov et al. 2013; Lan et al. 2020).

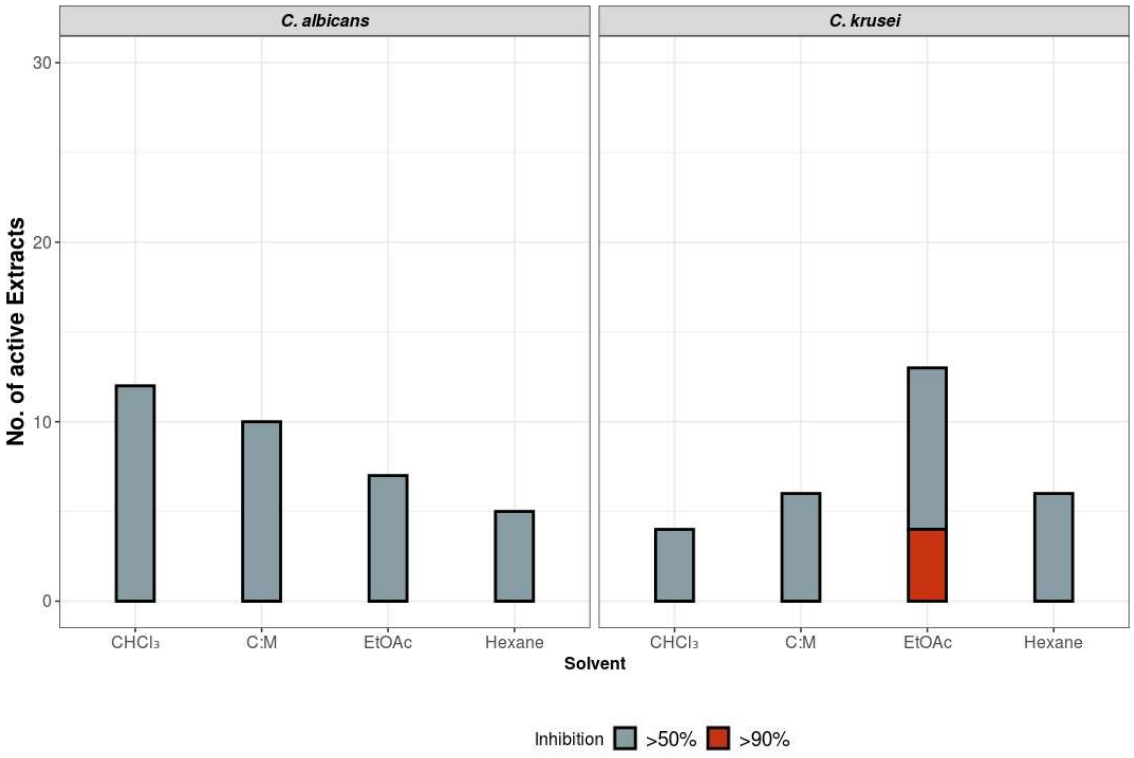

Figure 24. Summary of antifungal effects of endophytic extracts isolated from mosses (C:M - chloroform: MeOH (4:1) extract of mycelia).

6.3.4 Summary of investigations regarding the endophytic fungi isolated from *J. communis*, *A. asiatica* and mosses.

EF are highly diverse, and their investigation is very important from different plants to understand the biodiversity of the endophytic fungal community (Arnold et al. 2007). Given the high biodiversity of plants in Hungary, examining their fungal endophytes could lead to the discovery of novel metabolites. It is considered that biodiversity and structure of the endophytic fungal community mostly depends on the plant physiology, bio-geographical factors and their interplay with other pathogenic microbes associated with their host plant (Arnold et al. 2007).

The molecular identification was performed and a list of the identification results of EF isolates with their isolation source, collection code and GenBank accession number in NCBI, are summarized in Table S 1. In our study, the culture dependent method was followed for the molecular identification of fungi, which was carried out using ITS sequences. Although numerous studies reported that ITS is sufficient for species delimitation, it has several disadvantages in demonstrating intra-specific distances and at present, it is difficult to unify the ITS divergence for distinct fungal species (Raja et al. 2017). The availability of only a limited reference sequences in the databases and misidentifications of published sequences represents another difficulty restricting the identification of EF using ITS (Vilgalys, 2003). However, Arnold et al. reported delimited species of 72 Ascomycota and Basidiomycota, based on 90% sequence similarity of ITS genotype groups and showed that these sequences were concordant with 28S rDNA (Arnold et al. 2007).

Based on the ITS sequences, the isolates were characterized into 1 phylum, 3 classes, 10 orders and 2 isolates were identified only at the order level and 1 at family level. All of the isolated fungi belonged to the taxon Ascomycota, which includes three classes, Dothideomycetes and Sordariomycetes and Eurotiomycetes. In all three plants, Sordariomycetes was the dominant class followed by Dothideomycetes and Eurotiomycetes. Such dominance of Sordariomycetes as endophytes has also been reported from several plants eg. Phragmites (Sim et al. 2018) and lichens (U'Ren et al. 2016) indicating that Sordariomycetes are ubiquitous among the plant kingdoms.

Totally, 22 genera were identified involving *Alternaria, Aspergillus, Bipolaris, Cladosporium, Colletotrichum, Curvularia, Diaporthe, Dothiorella , Didymella, Clonostachys, Fusarium, Glomerella, Stemphylium, Simplicillium Purpureocillium, Phomopsis, Phoma, Penicillium, Pestalotiopsis, Trichoderma* and *Xylaria* (Figure 25, Table S 1). The relative abundance (RA) of all genera was analyzed in all three plants (Figure 25) and *Fusarium, Alternaria* and *Trichoderma* were most abundant in all cases.

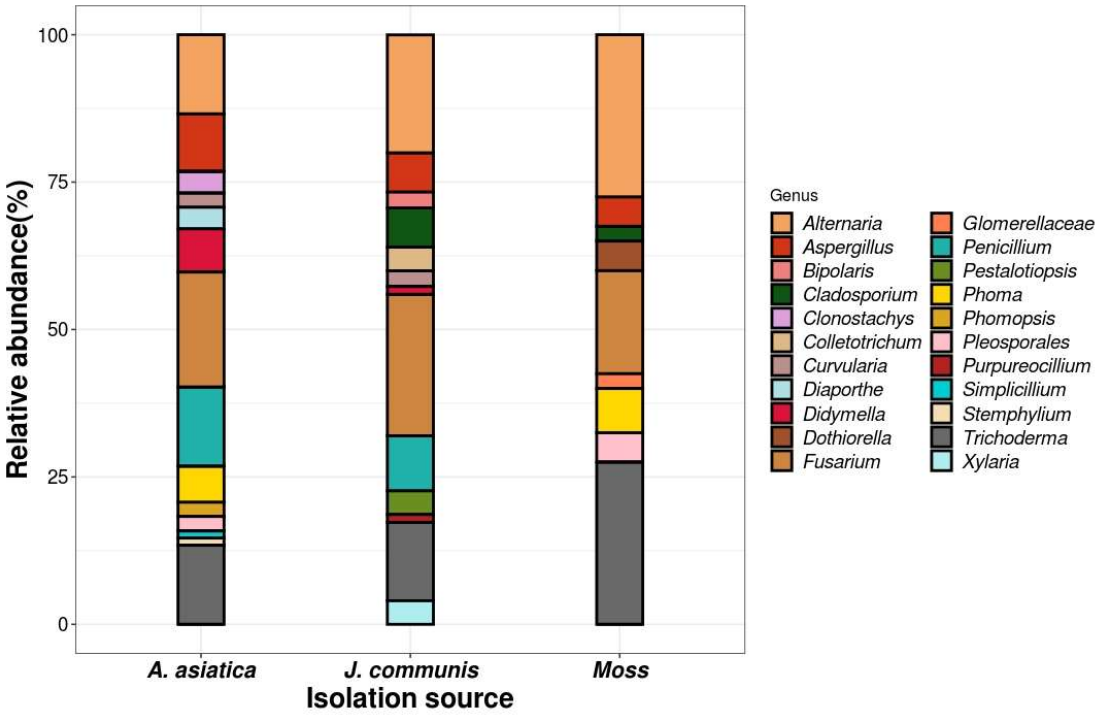

Figure 25. Relative abundance of EF from *A. asiatica*, *J. communis* and moss samples.

During the biodiversity examinations, *Bipolaris* sp. and *Purp. lilacinum* proved to be host specific within the examined sample set in *J. communis*. Previously the occurrence of *Purp. lilacinum* has been reported as endophyte in cotton aphids (Castillo et al. 2014).

Our findings revealed that the leaves and stem parts of the plants are excellent reservoirs for EF, where the most abundant were *Fusarium* and *Alternaria* and *Trichoderma* genera. Although, *Alternaria* and *Fuasrium* fungi are considered as plant pathogens, they might be latent, when they are inside the living tissues until the environmental conditions are favourable and might have evolved to endophytic lifestyle due to loss of virulence (Freeman and Rodrigues, 1993). These EF are gaining a lot of attention recently for their bioactive compounds (Toghueo et al. 2019; Hellwig et al. 2002; Kaushik et al. 2020).

In this work, *Phoma* strains could be identified only at the genus level and identified in all the three plants. The genus *Phoma* is ubiquitous and inhabits a diverse range of hosts, from soil to air, plants to animals (Aveskamp et al. 2010). Previously, extensive studies were carried to clarify the significant generic boundaries in Didymellaceae, however, due to the lack of phylogenetic

support of nearly 70 *Phoma* species belonging to Didymellaceae could not be assigned to definite genera (Aveskamp et al. 2010; de Gruyter et al. 2013; Chen et al. 2017). *Pestalotiopsis* species are the beneficial members of foliar endophytes as they have the capability to switch their nutritional-mode either by staying as an endophyte or becoming a saprobe (Maharachchikumbura et al. 2012; Douanla-Meli et al. 2013). In our study *Pestalotiopsis* species were identified only in *J. communis.* Although, *Pestalotiopsis* species are the most commonly found EF, it only represents 1.4 % in our study showing region specificity of this species. The members of the *Trichoderma* genus are found also dominant in our study. However, *Trichoderma* strains colonized abundantly in stems and cones of *A. asiatica* and *J. communis* and were not isolated from roots and leaves. In the literature, most of the studies reported the tissue specification of *Trichoderma* species to roots and leaves. In addition, the colonization mechanism of *Trichoderma* sp. was also reported through systemic infection, which proved that after the infection of roots the fungus could be re-isolated from stems rather than leaves and roots (Rosemana et al. 2018).

IR and RA of EF vary from plant to plant. In our cases, the IR of EF were found to be highest in stem, followed by leaf, whereas similar studies in other plants showed higher IR values in the leaf compared to stems (Alurappa and Chowdappa, 2018). The tissue and host specificity are also affected by different environmental conditions. Previous studies show that certain fungi such as *Aspergillus* (El-hawry et al. 2020) and *Penicillium* (Devi et al. 2012) did not exhibit host and tissue specificity, which was also found in our study.

Most of the pathogenic strains have become resistant to antibiotics and multi drug resistant strains have become a serious global health concern. Therefore, an intensive research is required for effective antimicrobial drugs. EF have been identified as an abundant reservoir of novel antimicrobial compounds (Strobel, 2003). One of the most important properties of EF is that they produce a wide variety of compounds that protect themselves from plant pathogens (Tan and Zou, 2001; Strobel, 2003). Secondary metabolites synthesized by EF have been reported as inhibitors of many animal and plant pathogens (Wiyakrutta et al. 2004; Gunatilaka, 2006; Zhao et al. 2011). From 2001 to 2019, there is a gradual increase in the number of patents registered related to EF. It has been reported that 224 patents were registered for secondary metabolites and 21 patents were related to biotransformation using EF. *Aspergillus*, *Fusarium*, *Trichoderma* and *Penicillium* are the

predominant genera with a higher number of patents for their bioactivity (Torres-Mendoza et al. 2020). In the present work 201 endophytic strains were isolated from medicinal plants and the antimicrobial activity of their metabolites was evaluated. A total of 112 (52%) strains showed antibacterial activity against at least one test strains. Altogether 23.11% of the isolates have antimicrobial effects with wide spectrum. Twelve strains showed remarkably high inhibitory percentage (>90%) against all of the tested strains.

Among the three solvents applied for the ferment broth extraction, EtOAC extracts were found to be more active. The EtOAC is by far the most common solvent used to extract bioactive compounds from EF (Selva kumar et al. 2018) and several studies showed that the EtOAC extracts showed higher antimicrobial activities in comparison to other solvent extracts (Thomas et al. 2011; Toghueo et al. 2020). However, using more than one different solvent, the extraction of different chemical profiles can be achieved. Thus, although, EtOAC extracts usually showed higher activity, certainly $CHCl_3$ extracts showed inhibition rates over them. Specifically, the $CHCl_3$ extracts of *Aspergillus* (SZMC 27164) isolated from *J. communis* showed higher activity against both Gram-positive bacteria and yeast, whereas the EtOAC extracts of the same strain showed no inhibition against those microorganisms. This suggests that the use of more than one solvent is important for screening bioactive metabolites produced by EF.

Furthermore, another significant observation in our study is that the bioactivity of fungal mycelial extracts could be comparably high as the ferment broth extracts and occasionally the inhibitory percentage is even higher than ferment broth extracts. Regarding the antifungal activity, 22 mycelial extracts were active against *C. albicans*, while 18 against *C. krusei*. Although there are numerous studies describing the antibacterial activity of extracellular metabolites (Meenupriya and Thangaraj, 2010) few studies have reported the bioactivity of intracellular compounds (Synytsya et al. 2017; Meenupriya and Thangaraj, 2010).

The extracts of *A. asiatica* endophytes were found to be possessing higher antimicrobial activity (Figure 20,Figure 21Table S 6, Table S 8, Table S 7, Table S 8, Table S 9).The antibacterial activity was higher than the antifungal activity. 43% of the extracts were active against bacteria, whereas only 12% were active against yeasts. *C. krusei* was found to be more susceptible than *C. albicans,* and regarding Gram-negative bacteria, especially *E. coli,* was highly sensitive to the extracts. The

Fusarium were the most predominant genus found to be exhibiting higher antibacterial activity than other isolates. Five out of 30 *Fusarium* strains had inhibitory activity against all the test organisms. Twenty, out of 30 *Fusarium* isolates were active against at least one of test organisms. Particularly, *Fusarium oxysporum* (SZMC 27185) and *Fusarium* sp. (SZMC 27188) isolated from *J. communis* showed more than 90% inhibitory activity against all test bacteria. Several studies have reported the antimicrobial potential of *Fusarium* sp. (Gherbawy and Elhariry, 2016; Liu et al.2012). It was isolated from *Tripterygium wilfordii* and produced the antimicrobial compounds subglutinol A and B (Liu, Wu, and Xu, 2007). It was also isolated from the bark of *Cinnamomum kanehirae* and produced beauvericin, which showed a strong inhibitory activity against methicillin-resistant *S. aureus* and *B. subtilis* (Wang et al. 2011). Furthermore, a *Fusarium* sp. isolated from *Selaginella pallescens* produced a pentaketide compound (2-methylbutyraldehyde-substituted-α-pyrone), which significantly suppressed the growth of *C. albicans* (Brady and Clardy, 2000). Besides *Fusarium* species, the metabolites of *Penicillium, Aspergillus, Pestalotiopsis, Trichoderma* and *Purpureocillium* species also showed strong activity against all the test pathogens. Metabolites of *Phoma* and *Didymella* exhibited higher antibacterial activity than antifungal activity. *Trichoderma* is another predominant genus producing metabolites, which exhibit high inhibitory activity. The important classes of secondary metabolites such as terpenes, anthraquinones, peptaibols and diketopiperazine like metabolites have been previously reported as *Trichoderma* products (Leylaie and Safari, 2018). It could be also observed that the isolated EF belonging in the same taxa could show different degrees of inhibition against test microorganisms. In the case of *Fusarium oxysporum*, *F. oxysporum* (SZMC 27184) showed no inhibition, whereas the SZMC 27185, SZMC 27186 strain of F. *oxysporum* exhibited inhibitory effect against all tested pathogens. This result strongly recommends that different strains from the same species cannot be ignored in examining their bioactivities.

7 CONCLUSIONS

In the present study, fungal endophytes were isolated from Hungarian medicinal plants (*H. perforatum*, *J. communis* and *A. asiatica*) and mosses. In the case of *H. perforatum* a chromatographic based screening was carried out to find host metabolite producing EF. Based on the results of analytical examinations (HPLC-UV) certain endophytes were able to produce the same metabolites as their plant hosts and thus, they can serve as novel microbial sources of bioactive plant metabolites. These metabolites were the hypericin, which is a medicinally important polyphenolic compound, and emodin, which is a biosynthetic precursor of hypericin in plants. The producer EF were the members of the genus *Alternaria* (producing emodin only) and a member of the genus *Epicoccum* (producing both emodin and hypericin). The *Alternaria* isolates were identified only at the section level, because members of the *A. alternata* species group including *A. tenuissima*, *A. arborescens*, and *A. alternata* cannot be discerned based either on the ITS sequence or on multigene approach. Furthermore, *E. nigrum* is anamorphic ascomycete distributed worldwide and considered to be a saprophytic fungus. Although it can also show an endophytic lifestyle and can be frequently isolated from the inner tissues of various plants. The identities of the host metabolites were confirmed via HPLC-HRMS technique based on the exact masses and MS2 fragmentation patterns and yield of the produced metabolites were determined in several cultivation conditions including illumination and cultivation media. In the case of the *E. nigrum* strain hypericin and emodin production ceased in the nineth generation and in the tenth generation, respectively, while the amount of emodin ceased completely from the tenth generation in the examined *Alternaria* strains. The addition of dried and fresh plant parts as an elicitor enhanced the biosynthesis of hypericin in the attenuated strains.

EF produce a plethora of secondary metabolites, which may open new avenues to study their applicability in pharmaceuticals. Despite the biotechnological potential of EF, the basic ecology about their relationship with the host plants is poorly understood. Therefore, in our study the fungal endophytic communities of *J. communis*, *A. asiatica* and several mosses were examined. The culturable EF were identified using molecular techniques and related to each plant group their biodiversity, richness, host and tissue specificity were described. As EF have been generally identified as an abundant reservoir of novel antimicrobial compounds, the antimicrobial activities

(antibacterial and antifungal) of the metabolites produced by the isolated fungi were extensively studied. Several extracts containing the endophytic metabolites proved to be active against the applied microorganisms. These isolates will be examined in detail in the future and the chemical nature of the active metabolites will be determined that may possibly lead to novel compounds for the pharmaceutical applications.

8 SUMMARY

Medicinal plants have been used in therapies for various illnesses from time immemorial. The use of natural sources for the prevention of illnesses is evident in many ancient cultures such as those of Indians, Chinese and North Africans, and was also recorded in Sumerian archeological remains (Phillipson 2001). Today, we are threatened with the extinction of many wild medicinal plant species due to the destruction of their anthropogenic habitat and to harvesting due to an increasing demand for plant metabolites. Besides, it is challenging to obtain bioactive compounds from plants due to technical difficulties such as long growth period, low yield and low level of accumulation (Chen et al. 2016). For instance, the accumulation of Taxol in *Taxus brevifolia* is 0.001–0.05% and to produce 1 kg of taxol, 15 kg of Taxus bark is needed (Malik et al. 2011). Therefore, it is important to find alternative approaches to produce medicinal plant-derived biologically active compounds, in particular, those derived from endangered or difficult-to-cultivate plant species to meet the medical demand. In this study we identified an endophytic fungus *E. nigrum* as an alternative source of the widely used antidepressant hypericin and also screened bioactive EF isolated from three different medicinal plants based on their antimicrobial activity.

This study was established to investigate the EF of Hungarian medicinal plants: *H. perforatum, A. asiatica, J. communis* and mosses. Results of this study were divided into 3 parts, isolation and molecular identification of EF, host metabolite producing ability of fungal endophytes from *H. perforatum* and screening of EF from other three plants for their bioactive potential.

In the targeted approach, the alternative source for the medically important compounds hypericin and emodin was the endophytic *E. nigrum,* and for emodin alone *Alternaria* sp. There are various challenges in exploiting EF for commercial utilization. To overcome the challenges; different parameters were employed to optimize the production of host metabolites in the producer strains. The strains were cultivated in different media including PDB, MEB, DM and CDB. The results revealed that PDB medium was found to be superior when compared to the other ones in terms of both biomass accumulation and host metabolite production in case of both SZMC 23769 and SZMC 23771. In order to check the stability of production for later commercial purposes, the strains were sub cultivated in different media. Our results on generation studies clearly indicated

that the strains SZMC 23769 and SZMC 23771 lost their ability to produce host metabolites during subsequent culturing. This is also dependent on the type of media used for the fermentation. In this case, DM and CDB were not suitable for increasing the production of metabolites over Sub-cultivations. Different strategies were employed to check whether the production ability of the attenuated strains could be restored and we found that the addition of dried and fresh plant parts of *H. perforatum* to the fermentation medium as an elicitor enhanced the synthesis of hypericin in an attenuated strain. It was also found that emodin could be used as an effective elicitor to stimulate the biosynthetic pathway of hypericin in our producer strain. It would be interesting to investigate the actual mechanism of biosynthesis in the future and to apply genomic and epigenomic strategies to stimulate the pathway in EF, which could provide opportunities for using our strain as a sustainable cell factory for hypericin synthesis.

In our work, altogether 254 strains from 406 plant fragments of *A. asiatica* (95), *J. communis* (132) and mosses (44) were isolated. The strains were selected for further investigations based on their culturable ability. The species, which showed slow growth and were not culturable under laboratory conditions were omitted and finally 82, 75 and 40 fungi were chosen from *A. asiatica*, *J. communis* and mosses, respectively for further investigations. *Trichoderma, Fusarium* and *Alternaria* species were found to be dominant in all three plants used for our investigation. However, by combining metagenomic approaches with traditional culture dependent isolation, the exact biodiversity of EF could be determined.

Regarding bioactivity, a total of 788 extracts were tested and 481 (61%) were found to be effective against at least one tested microorganism including 367 against *B. subtilis*, 341 against *S. aureus,* 221 against *E. coli* and 262 against *P. aeruginosa*. In the case of yeasts, *C. albicans* was susceptible to 92 extracts, and 63 extracts inhibited the growth of *C. krusei*. Interestingly, 36 extracts exerted antimicrobial activity against all bacteria and yeasts (>90%). However, none of the extracts did not show a remarkable activity against *R. solani* and *F. culmorum,* but few inhibited the growth of both phytopathogens, especially, *Purp. Lilacinum* (SZMC 27031) and *T. atroviride* (SZMC 27261). The detailed investigations of biocontrol metabolites of these fungi will be planned in the future. *Pestalotiopsis sp. D. glomerata, Aspergillus* sp. and *Purp. lilacinum* presented high inhibition against yeasts and further metabolomic investigation of these fungi could lead to the

identification of novel compounds with high therapeutic relevance. Summarizing the importance of the antimicrobial investigations, our work could serve as a base to explore the presence of novel bioactive compounds or even alternative sources for the existing ones.

As EF are a source of high bioactive compounds and phytochemicals, their bioprospecting could result in the discovery of a huge variety of novel therapeutic compounds. For the feasibility of using EF in commercial scale, it is essential to study the production kinetics of the active metabolites and to characterize the parameters effecting the production. Although, addition of plant-based elicitors and precursors was proved to restore the production ability, other approaches such as reversing the epigenetic silencing, metabolic reprogramming, and genome mining techniques would lead to overcome the problem of attenuation, which has been experienced also in our examinations.

In summary, our results corroborate, that the isolated and deposited fungal endophytes are excellent reservoirs of bioactive secondary metabolites, however further studies are needed to isolate the pure compounds from the screened strains. The presented results offer a proper framework of utilizing our isolates for their medical purposes.

9 ÖSSZEFOGLALÓ

A gyógynövények szerepe a különböző betegségek kezelésében nagy múltra tekint vissza. A természetes forrásból származó különleges vegyületek preventív és gyógyító hatását már a tradicionális gyógyászati rendszerekben is alkalmazták, melynek legkorábbi írott emléke a sumér homokkőtáblákon található, de ezen alapszik az indiai, kínai és észak-afrikai tradicionális orvoslás is (Phillipson 2001). Napjainkban számos vadon élő gyógynövényfaj kihalásával kell számolni egyrészt az antropogén hatások következtében kialakuló élőhely pusztulás miatt, másrészt pedig a növényi metabolitok iránti megnövekedett keresletet kielégítését célzó túlzó kitermelések következtében. További probléma a jelenkori gyógynövény hatóanyagokat tekintve, amely már a termesztett gyógynövények esetében is felmerülhet, hogy az utánpótlást biztosító növények gyakran hosszú növekedési ciklussal rendelkeznek, valamint, hogy kis mennyiségben tartalmazzák az egyes hatóanyagokat (Chen et al. 2016). A *Taxus brevifolia* esetében például a Taxol kihozatal 0.001–0.05%-os, azaz 1 kg hatóanyag előállításához 15 kg tiszafa kéreg szükséges (Malik et al. 2011). Ezért a gyógyszeriperi igényeknek megfelelve kiemelten fontos az új alternatív források felkutatása a növényi eredetű biológiailag aktív vegyületek előállításához, különösen olyan hatóanyagok esetében, melyek veszélyeztetett vagy nehezen termeszthető gyógynövényekből nyerhetők csak ki jelenleg. A munkánk során megoldást keresve a fenti kihívásokra, sikerrel izoláltunk egy *Epicoccum nigrum* endofiton gomba törzset, amely kutatásaink alapján új forrása lehet a széleskörben alkalmazott, antidepresszáns hatású hypericin vegyületnek, valamint feltérképeztük több endofiton gomba antimikrobiális hatású metabolit-termelő képességét.

A vizsgálatok alapját képező endofiton gombatörzsek izolálásához a *Hypericum perforatum, Artemisia asiatica, Juniperus communis* gyógynövényeket és különböző mohákat választottunk ki. A munka során elért eredményeket három fő részre lehet osztani, az első részben számoltunk be a *H. perforatum* növényből izolált, a növényi hatóanyagot termelni képes törzs felfedezéséről és a hatóanyag-termelés jellemzéséről. A második részben jellemeztük az *A. asiatica, J. communis* gyógynövényekből és mohákból izolált endofiton gombák biodiverzitását, valamint a harmadik részben áttekintést adtunk az izolátumok antimikrobiális metabolit termelő képességéről.

A célzott hatóanyag-vizsgálatok során azonosítottunk egy *E. nigrum* (SZMC 23769) törzset,

amely mind a hipericint, mind pedig a bioszintetikus előanyagát az emodint képes volt termelni, valamint két *Alternaria* (SZMC 23771, SZMC 23772) törzset melyek az emodint termelték. Az endofiton mikroorganizmusok alkalmazása a hatóanyag-termelésben azonban a termelés instabilitása miatt sokszor nehézségekbe ütközik, ezért megvizsgáltuk, hogy a törzseknél a tenyésztési paraméterek változtatása milyen hatással van a metabolitok hozamára. Az izolátumokat tenyésztettük burgonya-glükóz- (PDB), maláta kivonatos- (MEB), Czapek-Dox- (CDB) valamint szintetikus (DM) tápoldatokban, mely során mind a biomassza mennyiség mind pedig a hatóanyag kihozatal szempontjából a PDB tápközeg bizonyult a legelőnyösebb választásnak a vizsgált SZMC 23769 és SZMC 23771 izolátumok esetében. Ezt követően megvizsgáltuk, hogy a törzsek a különböző tápközegekben az egymást követő átoltások következtében elveszítik-e a metabolitok termelési képességét, vagy az stabilan fenntartható. Az egymást követő generációk termelési képesége fokozatosan csökkent mindkét vizsgált izolátumnál, mindkét vegyület esetében. A képesség elvesztésének kinetikája azonban jelentős függést mutatott a fermentáció során alkalmazott tápközeg minőségétől. Az SZMC 23769 törzs nem termelő generációjának felhasználásával különböző kísérleti beállításokat terveztünk a termelőképesség re-aktiválására. A vizsgálatban az előfermentációs közeghez adott szárított és frissen előkészített *H. perforatum* részek eredményesen indukálták a hipericin termelését, amely mérhető mennyiségben volt jelen az adott generáció, inducert nem tartalmazó környezetben fermentált tápközegében is. Hasonló indukciós hatás volt tapasztaltható, ha az emodint adalékoltuk az előtenyésztés során. A termelt hipericin mennyisége azonban mindkét esetben alacsonyabbnak bizonyult, mint a kiindulási generáció által termelt mennyiség. Kísérleteink alapján kijelenthető, hogy a termelés teljeskörű stabilizálásához további vizsgálatok szükségesek és valószínűleg a végső megoldást a bioszintézis mechanizmusának feltérképezése fogja jelenteni a jövőben, mely alapján tervezhetővé válik, hogy milyen genetikai és/vagy epigenetikai stratégiákat érdemes alkalmazni majd a stimulálás érdekében.

A kutatásaink második részében összesen 254 törzset izoláltunk *A. asiatica* (95), *J. communis* (132) és különböző mohák (44) 406 db növényi szegmenséből. Az izolálásokat táptalajon végeztük, így csak az úgynevezett „tenyészthető” endofiton gombák kerültek begyűjtésre, melyek közül kizártuk azokat a törzseket is, melyek növekedése túl lassú volt az alkalmazott körülmények között. Így végül 82 törzset izoláltunk az *A. asiatica* szegmensekről, míg

75-öt a *J. communis* növényi részekről és 40-et a mohnövényekről. Az ITS alapú molekuláris taxonómiai vizsgálatok alapján feltártuk a növényeket kolonizáló endofiton gombák biodiverzitását és meghatároztuk az egyes közösségek szerkezetét. A legdominánsabb fajoknak mindhárom növény esetében a *Trichoderma, Fusarium* és *Alternaria* nemzetség képviselői bizonyultak. A metagenomikai megközelítést az általunk is alkalmazott hagyományos tenyésztéses módszerrel kombinálva az endofiton gombák biodiverzitásáról részletesebb képet kaphattunk volna, azonban munkánk során arra törekedtünk, hogy azon gombák biodiverzitását mérjük fel, melyeknek a gyakorlat szempontjából is jelentőségük lehet. A nem tenyészthető endofitonok jelentősége vitathatatlan, azonban bioaktív képeségeik a tesztelhetőség hiányában jelenleg felfeddhetetlenek.

A bioaktivitási kísérletekben 788 extraktum antimikrobiális hatásait vizsgáltuk, mely során 481 extraktum (61%) bizonyult hatásosnak legalább egy tesztelt mikroorganizmussal szemben. A tesztek során 367 extraktum mutatott gátló hatást *Bacillus subtilis*, 341 *Staphylococcus aureus,* 221 *Escherichia coli* és 262 kivonat *Pseudomonas aeruginosa* baktériummal szemben. Az élesztők esetében 92 extraktum gátolta az alkalmazott *Candida albicans* törzset, míg 63 kivonat bizonyult aktívnak a *C. krusei* törzzsel szemben. Kiemelkedően magas antimikrobiális hatást (>90%) 36 kivonat tesztelése során tapasztaltunk, melyek egyaránt aktivak voltak a baktériumok és az élesztők gátlása során is. Azonban az is elmondható, hogy a fitopatogén gombákkal, a tesztekben alkalmazott *Rhizoctonia solani* és *Fusarium culmorum* törzsekkel szemben általában az extraktumoknál nem detektáltunk erőteljes gátló hatásokat. Ez alól csak néhány izolátum extraktuma volt kivétel, melyek közül kiemelkedtek a *Purpureocillium lilacinum* (SZMC 27031) és egy *Trichoderma atroviride* (SZMC 27031) izolátum aktivitásai. Klinikai jelentőségükre való tekintettel szintén érdemes megemlíteni négy izolátumot, melyek a *Pestalotiopsis, Didymella,* és *Aspergillus* nemzetség képviselői, valamint az előbb említett *Purp. lilacinum* törzs, mert extraktumaik mindkét élesztő esetében jelentős gátlóhatást mutattak. A hatástesztek során számos ígéretes, antimikrobiális metabolitot vagy metabolitokat termelni képes törzs került regisztrálásra, amely utat nyitott azok elválasztástechnikai vizsgálata felé, mely során új bioaktív vegyületek felfedezése vagy a már leírt vegyületek új forrásainak feltárása a cél.

10 ACKNOWLEDGEMENTS

I would like to express my heart felt gratitude to my supervisor, **Dr. András Szekeres** for his guidance, kindness and help during my research and thesis writing.

I express my heartfelt gratitude to the head of the department, **Prof. Dr. Csaba Vágvölgyi** for his support and providing me the funded extension to accomplish my Ph.D. degree and I am also thankful to head of the Institute of Biology, **Prof. Dr. Attila Gácser** for providing the workplace for my research.

I am also grateful to **László Bakacsy** from the Department of Plant Biology and **Anikó Németh** from the Botanical garden, University of Szeged for their help in plant collections.

I would like to acknowledge, **Prof. Dr. Judit Hohman** and **Dr. Dezső Csupor** from Department of Pharmacognosy for their contributions in the collection of the *A. asiatica* and moss samples,

I am extremely grateful to **Dr. Sándor Kocsubé** for his help in the phylogenetical examinations and for his valuable insights. I am also thankful to **Noémi kiss** for helping me in molecular identification experiments.

I extend my gratitude to **Dávid Rakk**, for his help in analytical experiments and for teaching me the techniques which instilled me to learn more in metabolomics. I am very thankful for my colleagues in lab 310 and 308, 312 for being kind and supportive. I also thank everyone in Department of Microbiology for providing me a friendly environment to work.

I am extremely grateful to Tempus foundation, Hungary and UGC, India for granting me Stipendium Hungaricum scholarship for pursuing my Ph.D in Hungary

I am forever indebted to all my friends who have helped me in many ways to support my stay in Hungary

Finally, I would like to acknowledge my family for all the support and love they have shown me through this period.

This work was supported by the Hungarian Government and the European Union within the frames of the Széchenyi 2020 Programme through grant GINOP-2.3.2-15-2016-00012. The infrastructural background was established with the support of GINOP-2.3.3-15-2016-00006 grant (Széchenyi 2020 Programme).

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12 LIST OF PUBLICATIONS RELATED TO THIS THESIS

A. Vigneshwari, D. Rakk, A. Németh, S. Kocsubé, N. Kiss, D. Csupor, T. Tamás, B. Škrbić, Cas. Vágvölgyi, A. Szekeres, 2019. Host metabolite producing endophytic fungi isolated from *Hypericum perforatum*. PLOS ONE 14 (5). doi:10.1371/journal.pone.0217060.

A, Vigneshwari, L. Abbas, L. Bakacsy, B. Škrbić, Cs. Vágvölgyi, A. Szekeres, 2018. Antimicrobial activities of the secondary metabolites of endophytic fungi isolated from *Juniperus communis*. In 16th Wellmann International Scientific Conference, 95–96.

A. Bartal, **A. Vigneshwari**, B. Bóka, M. Vörös, I. Takács, L. Kredics, L. Manczinger, M. Varga, Cs. Vágvölgyi, A. Szekeres, 2018. Effects of different cultivation parameters on the production of surfactin variants by a *Bacillus subtilis* strain. MOLECULES 23 (10). doi:10.3390/molecules23102675.

D, Rakk, **A. Vigneshwari**, B. Škrbić B, M. Varga, Cs. Vágvölgyi, A. Szekeres, 2018. Effect of different extraction methods on the metabolite profile of *Aspergillus* sp. isolated from *Juniperus communis*." In 16th Wellmann International Scientific Conference, 78–79.

A. Vigneshwari, D. Rakk, A. Németh, A. Csorba, T. Papp, Cs. Vágvölgyi, A. Szekeres, 2017. Endophytic Fungi Producing Bioactive Plant Metabolites. ACTA MICROBIOLOGICA HUNGARICA 64 (Supplement 1): 162.

A. Vigneshwari, D. Rakk, A. Németh, A. Csorba, T. Papp, Cs. Vágvölgyi, A. Szekeres, 2017. Endofiton gombák által termelt növényi metabolitok vizsgálata - Plant metabolites production by fungal endophytes." MIKOLÓGIAI KÖZLEMÉNYEK-CLUSIANA 56 (1): 27–29.

A. Vigneshwari, 2017. Endophytic fungi producing valuable host metabolites. ACTA MICROBIOLOGICA ET IMMUNOLOGICA HUNGARICA 64 (Supplement 1): 162.

A. Vigneshwari, A. Németh, L. Kredics, Cs. Vágvölgyi, A. Szekeres, 2016. Production of host metabolites by endophytes of *Hypericum perforatum*. In A Magyar Mikrobiológiai Társaság 2016. Évi Nagygyűlése És a XII. Fermentációs Kollokvium, 66–67.

A. Vigneshwari, O. Bencsik, T. Marik, A. Németh, L. Kredics, Cs. Vágvölgyi, A. Szekeres, 2016.

Isolation of endophytic fungi from medicinal plants. In International Conference on Science and Technique Based on Applied and Fundamental Research (ICoSTAF'16), 46.

A. Vigneshwari, O. Bencsik, T. Marik, G.Z. Elek, A. Németh, L. Kredics, Cs. Vágvölgyi, A. Szekeres, 2016. Characterisation of endophytic fungi isolated from *Hypericum perforatum*. In 18th Danube-Kris-Mures-Tisa (DKMT) Euroregional Conference on Environment and Health, 97.

13 SUPPLEMENTARY MATERIAL

Table S 1. EFs isolated in this study

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
A. asiatica		Leaf	*Alternaria sp*	SZMC 27067	MT879608
A. asiatica		Leaf	*Alternaria sp*	SZMC 27068	MT879609
A. asiatica		Leaf	*Alternaria sp*	SZMC 27069	MT879610
A. asiatica		Leaf	*Alternaria sp*	SZMC 27070	MT879611
A. asiatica		Leaf	*Alternaria sp*	SZMC 27071	MT879612
A. asiatica		Leaf	*Alternaria sp*	SZMC 27072	MT879613
A. asiatica		Leaf	*Alternaria sp*	SZMC 27073	MT879614
A. asiatica		Leaf	*Alternaria sp*	SZMC 27074	MT879615
A. asiatica		Leaf	*Alternaria sp*	SZMC 27075	MT879616
A. asiatica		Stem	*Aspergillus sp*	SZMC 27076	MT994591
A. asiatica		Stem	*Aspergillus sp*	SZMC 27077	MT994592
A. asiatica		Leaf	*Aspergillus sp*	SZMC 27078	MT994593

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
A. asiatica		Stem	*Aspergillus flavus*	SZMC 27079	MT994594
A. asiatica		Stem	*Aspergillus fumigatus*	SZMC 27080	MT994595
A. asiatica		Stem	*Aspergillus sp*	SZMC 27081	MT994596
A. asiatica		Stem	*Aspergillus sp*	SZMC 27082	MT994597
A. asiatica		Stem	*Aspergillus sp*	SZMC 27083	MT994598
A. asiatica		Stem	*Clonostachys rosea*	SZMC 27084	MT883288
A. asiatica		Stem	*Cladosporium sp*	SZMC 27085	MT883289
A. asiatica		Stem	*Cladosporium sp*	SZMC 27086	MT883290
A. asiatica		Stem	*Cladosporium sp*	SZMC 27087	MT883291
A. asiatica		Stem	*Cladosporium sp*	SZMC 27088	MT883292
A. asiatica		Stem	*Cladosporium sp*	SZMC 27089	MT883293
A. asiatica		Leaf	*Penicillium sp*	SZMC 27090	MT994617
A. asiatica		Stem	*Clonostachys rosea*	SZMC 27091	MT940229
A. asiatica		Leaf	*Clonostachys rosea*	SZMC 27092	MT940230
A. asiatica		Leaf	*Curvularia lunata*	SZMC 27093	MT994617

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
A. asiatica		Leaf	*Curvularia lunata*	SZMC 27094	MT994617
A. asiatica		Leaf	*Diaporthe sp*	SZMC 27095	MT940231
A. asiatica		Leaf	*Diaporthe sp*	SZMC 27096	MT940232
A. asiatica		Leaf	*Diaporthe sp*	SZMC 27097	MT940233
A. asiatica		Leaf	*Didymella sp*	SZMC 27098	MT940234
A. asiatica		Leaf	*Didymella sp*	SZMC 27099	MT940235
A. asiatica		Leaf	*Didymella sp*	SZMC 27100	MT940236
A. asiatica		Leaf	*Didymella glomerata*	SZMC 27101	MT940237
A. asiatica		Leaf	*Didymella glomerata*	SZMC 27102	MT940238
A. asiatica		Leaf	*Didymella glomerata*	SZMC 27103	MT994617
A. asiatica		Stem	*Alternaria sp*	SZMC 27104	MT997192
A. asiatica		Stem	*Alternaria sp*	SZMC 27105	MT997193
A. asiatica		Stem	*Fusarium circinatum*	SZMC 27106	MT997194
A. asiatica		Stem	*Fusarium circinatum*	SZMC 27107	MT997195

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
A. asiatica		Leaf	*Fusarium oxysporum*	SZMC 27108	MT997196
A. asiatica		Leaf	*Fusarium oxysporum*	SZMC 27109	MT997197
A. asiatica		Leaf	*Fusarium oxysporum*	SZMC 27110	MT997198
A. asiatica		Stem	*Fusarium sp*	SZMC 27111	MT881636
A. asiatica		Stem	*Fusarium sp*	SZMC 27112	MT881637
A. asiatica		Leaf	*Fusarium sp*	SZMC 27113	MT881638
A. asiatica		Stem	*Fusarium sp*	SZMC 27114	MT881639
A. asiatica		Leaf	*Fusarium sp*	SZMC 27115	MT997199
A. asiatica		Leaf	*Penicillium chrysogenum*	SZMC 27116	MT997200
A. asiatica		Leaf	*Penicillium hordeii*	SZMC 27117	MT997201
A. asiatica		Leaf	*Penicillum sp*	SZMC 27118	MT997202
A. asiatica		Leaf	*Penicillum sp*	SZMC 27119	MT994761
A. asiatica		Leaf	*Penicillum sp*	SZMC 27120	MT994762
A. asiatica		Stem	*Penicillum sp*	SZMC 27121	MT994763

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
A. asiatica		Leaf	*Penicillum sp*	SZMC 27122	MT994764
A. asiatica		Leaf	*Penicillum sp*	SZMC 27123	MT994765
A. asiatica		Leaf	*Phomopsis sp*	SZMC 27124	MT994766
A. asiatica		Leaf	*Phoma sp*	SZMC 27125	MT994650
A. asiatica		Leaf	*Phoma sp*	SZMC 27126	MT994651
A. asiatica		Leaf	*Phomopsis sp*	SZMC 27127	MT994652
A. asiatica		Stem	*Phomopsis sp*	SZMC 27128	MT994653
A. asiatica		Leaf	*Pleosporales sp*	SZMC 27129	MT994654
A. asiatica		Leaf	*Simplicillium sp*	SZMC 27130	MT994655
A. asiatica		Stem	*Stemphylium sp*	SZMC 27131	MT994656
A. asiatica		Stem	*Trichoderma sp*	SZMC 27132	MT881591
A. asiatica		Stem	*Trichoderma harzianum*	SZMC 27133	MT881592
A. asiatica		Stem	*Trichoderma sp*	SZMC 27134	MT994657
A. asiatica		Stem	*Trichoderma sp*	SZMC 27135	MT881593
A. asiatica		Stem	*Trichoderma sp*	SZMC 27136	MT881594
A. asiatica		Stem	*Trichoderma atroviride*	SZMC 27137	MT881595
A. asiatica		Stem	*Trichoderma sp*	SZMC 27138	MT881596

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
A. asiatica		Leaf	*Trichoderma sp*	SZMC 27139	MT881597
A. asiatica		Stem	*Trichoderma sp*	SZMC 27140	MT881598
A. asiatica		Stem	*Trichoderma sp*	SZMC 27141	MT881599
A. asiatica		Stem	*Trichoderma sp*	SZMC 27142	MT881600
A. asiatica		Stem	*Phoma sp*	SZMC 27143	MT994658
A. asiatica		Stem	*Phoma sp*	SZMC 27144	MT994659
A. asiatica		Stem	*Phoma sp*	SZMC 27145	MT994660
A. asiatica		Stem	*Pleosporales sp*	SZMC 27146	MT994661
A. asiatica		Stem	*Fusarium lateritium*	SZMC 27147	MT994662
A. asiatica		Stem	*Fusarium sporotrichiodes*	SZMC 27148	MT994661
A. asiatica	N 46°53.338' E 019°24.483'	Stem	*Alternaria sp*	SZMC 27149	MT940776
J. communis	N 46°53.340' E 019°24.528'	Stem	*Alternaria sp*	/SZMC 27150	MT940777
J. communis	N 46°53.340' E 019°24.528'	Stem	*Alternaria sp*	SZMC 27151	MT940778
J. communis	N 46°53.338' E 019°24.483'	Stem	*Alternaria sp*	SZMC 27152	MT940779
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27153	MT940780
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27154	MT940781
J. communis	N 46°53.345' E 019°24.501'	Leaf	*Alternaria sp*	SZMC 27155	MT940782

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27156	MT940783
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27157	MT940784
J. communis	N 46°53.338' E 019°24.483'	Leaf	*Alternaria sp*	SZMC 27158	MT940785
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27159	MT940786
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27160	MT940787
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27161	MT940788
J. communis	N 46°53.345' E 019°24.501'	Stem	*Alternaria sp*	SZMC 27162	MT940789
J. communis	N 46°53.338' E 019°24.483'	Stem	*Alternaria sp*	SZMC 27163	MT940790
J. communis	N 46°53.345' E 019°24.501'	Stem	*Aspergillus fumigatus*	SZMC 27164	MT993364
J. communis	N 46°53.345' E 019°24.501'	Stem	*Aspergillus sp*	SZMC 27165	MT993365
J. communis	N 46°53.338' E 019°24.483'	Stem	*Aspergillus sp*	SZMC 27166	MT993366
J. communis	N 46°53.345' E 019°24.501'	Stem	*Aspergillus sp*	SZMC 27167	MT993367
J. communis	N 46°53.345' E 019°24.501'	Stem	*Aspergillus sp*	SZMC 27168	MT993368
J. communis	N 46°53.330' E 019°24.478'	Stem	*Cladosporium sp*	SZMC 27169	MT993369
J. communis	N 46°53.330' E 019°24.478'	Stem	*Cladosporium sp*	SZMC 27170	MT993370
J. communis	N 46°53.330' E 019°24.478'	Stem	*Cladosporium sp*	SZMC 27171	MT993371
J. communis	N 46°53.338' E 019°24.483'	Stem	*Cladosporium sp*	SZMC 27172	MT993372
J. communis	N 46°53.330' E 019°24.478'	Root	*Cladosporium sp*	SZMC 27173	MT994503

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
J. communis	N 46°53.330' E 019°24.478'	Stem	*Colletotrichum sp*	SZMC 27174	MT994504
J. communis	N 46°53.330' E 019°24.478'	Leaf	*Colletotrichum sp*	SZMC 27175	MT994505
J. communis	N 46°53.330' E 019°24.478'	Stem	*Colletotrichum sp*	SZMC 27176	MT994506
J. communis	N 46°53.342' E 019°24.474'	Stem	*Curvularia lunata*	SZMC 27177	MT994507
J. communis	N 46°53.330' E 019°24.478'	Stem	*Curvularia lunata*	SZMC 27178	MT994508
J. communis	N 46°53.330' E 019°24.478'	Stem	*Didymella glomerata*	SZMC 27179	MT994509
J. communis	N 46°53.338' E 019°24.483'	Stem	*Fusarium accuminatum*	SZMC 27180	MT994510
J. communis	N 46°53.342' E 019°24.474'	Stem	*Fusarium accuminatum*	SZMC 27181	MT994511
J. communis	N 46°53.340' E 019°24.528'	Stem	*Fusarium accuminatum*	SZMC 27182	MT994512
J. communis	N 46°53.338' E 019°24.483'	Leaf	*Fusarium accuminatum*	SZMC 27183	MT994513
J. communis	N 46°53.342' E 019°24.474'	Root	*Fusarium oxysporum*	SZMC 27184	MT982177

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium oxysporum*	SZMC 27185	MT982178
J. communis	N 46°53.338' E 019°24.483'	Root	*Fusarium oxysporum*	SZMC 27186	MT982179
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium oxysporum*	SZMC 27187	MT982180
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium sp*	SZMC 27188	MT982181
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium sp*	SZMC 27189	MT982182
J. communis	N 46°53.338' E 019°24.483'	Root	*Fusarium sp*	SZMC 27190	MT982183
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium sp*	SZMC 27191	MT982184
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium sp*	SZMC 27192	MT982185
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium sp*	SZMC 27193	MT982186
J. communis	N 46°53.342' E 019°24.474'	Root	*Fusarium sp*	SZMC 27194	MT982187
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium sp*	SZMC 27195	MT982188
J. communis	N 46°53.340' E 019°24.528'	Root	*Fusarium sp*	SZMC 27196	MT982189
J. communis	N 46°53.338' E 019°24.483'	Root	*Penicillum sp*	SZMC 27197	MT982190
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Penicillum sp*	SZMC 27198	MT982191
J. communis	N 46°53.342' E 019°24.474'	Leaf	*Penicillium citrinum*	SZMC 27199	MT982192

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Penicillium citrinum*	SZMC 27200	MT982193
J. communis	N 46°53.338' E 019°24.483'	Leaf	*Penicillium chrysogenum*	SZMC 27201	MT982194
J. communis	N 46°53.342' E 019°24.474'	Leaf	*Penicillum sp*	SZMC 27202	MT982195
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Penicillum sp*	SZMC 27203	MT982196
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Pestalotiopsis sp*	SZMC 27204	MT982197
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Pestalotiopsis sp*	SZMC 27205	MT982198
J. communis	N 46°53.338' E 019°24.483'	Leaf	*Pestalotiopsis sp*	SZMC 27206	MT982199
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Bipolaris sp*	SZMC 27207	MT982200
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Bipolaris sp*	SZMC 27208	MT982201
J. communis	N 46°53.338' E 019°24.483'	Leaf	*Phomopsis sp*	SZMC 27209	MT982202
J. communis	N 46°53.340' E 019°24.528'	Leaf	*Trichoderma sp*	SZMC 27210	MT997192
J. communis	N 46°53.342' E 019°24.474'	Leaf	*Trichoderma sp*	SZMC 27211	MT997193
J. communis	N 46°53.342' E 019°24.474'	Cone	*Trichoderma sp*	SZMC 27212	MT997194
J. communis	N 46°53.342' E 019°24.474'	Cone	*Trichoderma sp*	SZMC 27213	MT997195
J. communis	N 46°53.342' E 019°24.474'	Cone	*Trichoderma sp*	SZMC 27214	MT997196
J. communis	N 46°53.342' E 019°24.474'	Cone	*Trichoderma sp*	SZMC 27215	MT997197
J. communis	N 46°53.338' E 019°24.483'	Cone	*Trichoderma sp*	SZMC 27216	MT997198

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
J. communis	N 46°53.342' E 019°24.474'	Cone	*Trichoderma sp*	SZMC 27217	MT997199
J. communis	N 46°53.342' E 019°24.474'	Cone	*Trichoderma sp*	SZMC 27218	MT997200
J. communis	N 46°53.340' E 019°24.528'	Cone	*Trichoderma sp*	SZMC 27219	MT997201
J. communis	N 46°53.340' E 019°24.528'	Cone	*Xyaria digitata*	SZMC 27220	MT997202
J. communis	N 46°53.338' E 019°24.483'	Cone	*Xyaria digitata*	SZMC 27221	MT997203
J. communis	N 46°53.338' E 019°24.483'	Cone	*Xyaria sp*	SZMC 27222	MT997204
J. communis	N 46°53.338' E 019°24.483'	Stem	*Purpureocillium lilacinum*	SZMC 27031	MT997205
J. communis	N 46°53.340' E 019°24.528'		*Alternaria sp*	SZMC 27223	MT872076
Mosses			*Alternaria sp*	SZMC 27224	MT872077
Mosses			*Alternaria sp*	SZMC 27225	MT994749
Mosses			*Alternaria sp*	SZMC 27226	MT873032
Mosses			*Alternaria sp*	SZMC 27227	MT873033
Mosses			*Alternaria sp*	SZMC 27228	MT873034
Mosses			*Alternaria sp*	SZMC 27229	MT873035
Mosses			*Alternaria sp*	SZMC 27230	MT873036
Mosses			*Alternaria sp*	SZMC 27231	MT873037
Mosses			*Alternaria sp*	SZMC 27232	MT872025
Mosses			*Alternaria sp*	SZMC 27233	MT873038

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
Mosses			*Aspergillus sp*	SZMC 27234	MT874055
Mosses			*Aspergillus sydowii*	SZMC 27235	MT874056
Mosses			*Phoma sp*	SZMC 27236	MT994750
Mosses			*Cladosporium sp*	SZMC 27237	MT994751
Mosses			*Dothiorella gregaria*	SZMC 27238	MT874057
Mosses			*Dothiorella gregaria*	SZMC 27239	MT874058
Mosses			*Fusarium sp*	SZMC 27240	MT994752
Mosses			*Fusarium cerealis*	SZMC 27241	MT874059
Mosses			*Fusarium cerealis*	SZMC 27242	MT874060
Mosses			*Fusarium sp*	SZMC 27243	MT994753
Mosses			*Fusarium oxysporum*	SZMC 27244	MT994754
Mosses			*Fusarium sp*	SZMC 27245	MT994755
Mosses			*Fusarium sp*	SZMC 27246	MT994756
Mosses			*Glomerellaceae*	SZMC 27247	MT994757
Mosses			*Phoma sp*	SZMC 27248	MT994758

Plant	GPS coordinates if available	Plant part	Species	Collection code	Genbank ID
Mosses			*Phoma sp*	SZMC 27249	MT994759
Mosses			*Pleosporales sp*	SZMC 27250	MT997891
Mosses			*Pleosporales sp*	SZMC 27251	MT997892
Mosses			*Trichoderma atroviride*	SZMC 27252	MT997893
Mosses			*Trichoderma atroviride*	SZMC 27253	MT997894
Mosses			*Trichoderma citrinoviride*	SZMC 27254	MT997895
Mosses			*Trichoderma longibrachiatum*	SZMC 27255	MT997896
Mosses			*Trichoderma sp*	SZMC 27256	MT997897
Mosses			*Trichoderma sp*	SZMC 27257	MT997898
Mosses			*Trichoderma sp*	SZMC 27258	MT997899
Mosses			*Trichoderma sp*	SZMC 27259	MT997900
Mosses			*Trichoderma viride*	SZMC 27260	MT997901
Mosses			*Trichoderma atroviride*	SZMC 27261	MT997902
Mosses			*Trichoderma sp*	SZMC 27262	MT997903

Table S 2. Antimicrobial effects of EFs' metabolites of *J. communis* extracted with chloroform from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27149	95.41±13.2	16.53±16.2	43.45±12.9	25.85±10.5	24.73±5	6.3±3.1
SZMC 27150	15.67±1.6	49.15±12.4	42.64±14.5	11.62±1.6	37.98±2.9	8.95±14.3
SZMC 27151	99.7±11.2	49.1±16.1	33.93±6.8	30.88±4.4	41.31±13.5	6.59±11.4
SZMC 27152	76.76±15.6	86.52±11.4	1.12±3.1	47.29±7.5	45.2±8.3	14.97±12.4
SZMC 27153	65.47±3.9	76.51±13.1	45.36±11	15.6±3.3	18.39±2.4	46.96±4.7
SZMC 27154	66.51±3.4	81.79±11.7	32.02±3.3	44.79±9.6	20.67±14.7	19.13±1.5
SZMC 27155	79.71±15.1	99.19±10.2	6.38±14.3	21.46±6.1	25.37±2.3	12.63±4.2
SZMC 27156	77.94±5.1	91.61±15.6	45.15±5	10.4±2.5	39.59±5.5	38.7±6.3
SZMC 27157	51.57±16.2	86.33±10.7	25.09±5.5	21.78±11.4	15.99±9.3	1.39±8.5
SZMC 27158	67.46±5.3	42.38±16.3	43.02±15.2	32.5±12.7	46.66±1.5	24.39±14.6
SZMC 27159	77.67±15.9	77±1.5	31.44±13.7	20.2±2.2	15.56±16.2	18.84±14.8
SZMC 27160	46.67±7.1	78.67±9.4	45.01±11.2	5.94±2.1	45.9±12.5	10.61±8
SZMC 27161	6.77±3.6	81.67±6.9	24.13±16.4	36.02±6.7	22.81±5.2	0.91±6.2
SZMC 27162	79.06±12.1	49.72±10.6	8.24±16.2	8.48±3.3	47.54±14.5	23.01±11.2
SZMC 27163	97.7±11.7	32.01±9.6	9.15±11.7	29.38±9.1	18.46±11.5	58.96±14.8
SZMC 27164	96.15±12.2	94.04±13.2	90.43±4.6	90.02±1.2	86.53±6.7	94.38±15.3

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27165	11.91±10.2	70.76±2.8	36.64±1.9	64.36±8.4	94.26±10	52.85±1.1
SZMC 27166	97.7±6.5	77.33±7	23.36±11.7	47.25±15.9	28.39±15.7	28.85±1.4
SZMC 27167	76.4±2.5	85.8±2.6	24.92±10.8	28.11±15.6	81.22±2.6	82.69±7.4
SZMC 27168	69.76±12	13.36±7.1	50.44±14.5	78.93±8.5	30.2±11.7	97.9±11.3
SZMC 27169	56.71±3.3	62.23±1.1	80.11±6.7	16.23±2.7	50.93±15.4	26.7±6.6
SZMC 27170	71.69±2.3	49.28±12.4	28.51±15.9	13.16±13.3	81.96±13	14.82±8.3
SZMC 27171	70.46±3.9	85.39±12.6	30.82±3.8	17.08±7.8	50.54±6.3	74.29±7
SZMC 27172	44.74±8.8	77±7.9	68.23±10	14.31±5.3	43.43±11.7	52.24±7.6
SZMC 27173	61.6±11.6	29.21±9.3	35.41±14.4	54.29±9.9	69.91±10.7	41.32±6.9
SZMC 27174	71.55±3.3	43.38±1.4	60.93±14.4	32.02±3.7	14.35±2.9	33.81±15
SZMC 27175	79.91±7.7	18.16±8.7	41.66±9	13.48±4.6	84.94±2.8	26.64±2.4
SZMC 27176	70.77±4.7	29.09±6.9	44.64±5.5	98.97±15.2	97.05±10.6	34.38±3.3
SZMC 27177	96.49±14.7	68.21±12	34.43±2.8	60.16±1.9	83.51±13.5	43.75±5.2
SZMC 27178	40.54±6.8	41.67±5.1	14.44±6.5	55.36±10.4	95.67±15.7	23.42±11.6
SZMC 27179	77.54±13.1	70.46±5.3	89.3±7.5	71.99±7.5	21.58±11.8	0.87±5.6
SZMC 27180	70.76±11.9	55.89±8.9	42.53±2.3	66.69±8.5	12.03±13.6	24.8±13.2
SZMC 27181	97.44±10.8	5.71±6.6	95.59±12.4	36.96±13.9	62.61±5	53.79±9.1
SZMC 27182	7.64±14.9	14.09±14.4	69.14±7.5	76.43±5.3	71.06±9.1	51.22±11.2
SZMC 27183	7.46±11.9	77.8±7.9	34±5.5	19.07±8	16.43±8.4	44.53±8.4

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27184	29.57±14.7	4.92±13.2	44.65±12.3	28.45±9.8	0.29±2.2	26.86±2.2
SZMC 27185	91.6±3.4	79.51±8.7	13.66±14.3	19.87±10.9	54.24±6.3	6.06±10.6
SZMC 27186	79.77±3.8	53.77±6.3	21.95±13.7	78.08±11.2	86.87±11.5	94.41±13.8
SZMC 27187	79.97±15.9	8.98±9.3	62.43±3.6	86.34±15.2	79.54±5	53.95±7
SZMC 27188	66.76±4.7	30.93±4.7	16.43±9.4	60.41±8.1	46.08±2.4	61.1±11.7
SZMC 27189	77.79±12	93.43±16	42.54±12.9	66.26±12.7	44.87±10.8	76.73±11.6
SZMC 27190	77.96±8.5	7.97±3.8	4.84±11.7	82.22±8.2	82.35±12.4	35.24±15.2
SZMC 27191	96.49±15.9	6.16±9	54.19±6	3±3.4	80.2±7.9	16.53±6.3
SZMC 27192	77.16±9.9	11.18±5.2	43.43±13.8	26.11±13.1	3.33±7.8	25.88±5.1
SZMC 27193	7.91±11.5	80.23±2.4	43.12±7.7	12.84±14.7	37.27±12.1	64.21±2.7
SZMC 27194	76.05±16	22.37±8.5	66.89±3.1	74.31±7.4	33.22±13.8	92.59±6.4
SZMC 27195	65.67±4	53.45±4.2	61.45±4	32.27±3.3	66.14±8.4	53.54±12.4
SZMC 27196	79.17±14.9	27.52±15.5	19.88±15.7	84.81±1.1	39.44±10.2	16.08±3.1
SZMC 27197	71.17±14.6	32.35±8.5	1.35±14.3	64.61±14.3	12.93±4	38.59±2.6
SZMC 27198	79.66±6.9	32.98±6.3	65.18±4.6	45.61±6.5	11.49±13.8	31.82±3
SZMC 27199	5.4±13.9	46.54±6	22.83±10.3	72.02±14.8	50.66±6.6	39.63±13.5
SZMC 27200	59.57±8.6	90.11±9	64.81±12.5	70.74±3.6	37.03±11.8	33.34±2.6
SZMC 27201	47.55±6.4	8.57±12.9	18.68±13.2	43.25±6.8	29.39±9	3.66±7.1
SZMC 27202	74.19±13.4	61.28±2.5	42.69±2.2	17.93±6.9	71.37±2.8	23.87±5.8

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27203	6.06±3.9	65.15±15.9	93.84±6.3	3.18±5.2	29.9±9.6	28.84±14.6
SZMC 27204	6.79±5.8	83.72±11.5	43.49±9.1	46.69±12.2	9.51±7.2	0.48±9.4
SZMC 27205	96.71±9.5	92.12±9.9	85.36±4.4	92.76±11	96.05±1.2	87.78±11.4
SZMC 27206	56.75±13.9	72.13±14.4	66.28±16.2	44.43±3	61.67±13.8	37.24±12.5
SZMC 27207	57.65±13.5	8.28±12.1	86.49±9.8	12.24±5.5	35.66±6.8	43.14±8.8
SZMC 27208	49.16±8.3	3.61±13.6	54.25±6.1	21.03±3	23.95±3	34.6±11.6
SZMC 27209	44.17±15.2	78.14±15.2	55±1.5	26.05±10.1	53.59±14.6	46.44±14.5
SZMC 27210	36.46±15.7	49.21±7.5	13.29±14.9	59.15±10	34.76±11.2	43.06±9.3
SZMC 27211	56.47±13.7	13.33±14.6	24.14±2.5	28.28±6	44.95±2.1	45.5±4.3
SZMC 27212	65.77±10.5	55.78±15.3	9.21±16.2	33.65±8.3	39.51±12.6	28.95±13.1
SZMC 27213	67.67±3.5	2.41±7.3	63.24±12.5	57.19±4.6	70.24±12	16.84±2.1
SZMC 27214	70.66±12.8	92.07±2.3	61.88±16.4	75.91±15.1	41.75±3.5	11.63±6.4
SZMC 27215	6.61±15.1	31.95±1.2	40.84±9.8	1.24±9.1	74.01±14.3	39.12±4.7
SZMC 27216	27.66±1.6	80.21±7.4	44.1±2.7	36.31±14.8	33.21±2.6	95.74±14.2
SZMC 27217	66.66±11.9	45.03±11.7	2.41±9.6	10.45±9.2	24.5±10.7	17.75±7
SZMC 27218	76.6±14	45.65±2.3	49.4±3.9	79.41±8.4	59.05±6.3	29.99±1.2
SZMC 27219	94.65±12.1	32.87±7	96.22±12.1	43.84±13	30.31±11.5	36.52±12.4
SZMC 27220	6.46±15.8	2.42±5.1	58.34±3.4	62.5±7.5	14.5±15.3	43.9±10.8
SZMC 27221	37.75±8.3	92.68±11.9	46.49±4.1	68.72±8.1	12.06±6.9	4.91±6.8

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27222	47.76±12.4	47.41±5.2	11.34±15.5	7.91±11.4	20.88±7	37.2±1.5
SZMC 27031	97.16±1.8	89.41±9.4	8.9±1.1	26.27±4.4	53.98±14.3	12.5±8.2

Table S 3. Antimicrobial effects of EFs' metabolites of *J. communis* extracted with ethyl acetate from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27149	5.6±3.5	77.44±9	54.35±10.3	54.88±11.3	25.85±12.8	14.5±5.6
SZMC 27150	6.59±13.7	59.56±5.8	30.54±7.9	46.26±1.4	51.62±16.3	19.44±11.1
SZMC 27151	52.7±4.4	58.19±10	44.44±14.3	42.66±2.9	30.88±8.7	54.35±12.7
SZMC 27152	5.21±11	18.35±10.1	30.36±7.1	24.24±14.4	47.29±15.9	67.3±16
SZMC 27153	60.88±8	76.18±3.3	52.4±6	46.92±1.7	15.6±11.6	75.02±15.5
SZMC 27154	56.78±11.9	1.22±12	11.13±2.3	96.24±12.1	44.79±3	15.89±2.2
SZMC 27155	68.06±11.4	95.11±13.3	85.41±10	1.46±4.5	71.46±5.7	75.4±11.2
SZMC 27156	77.19±15.4	87.04±1.3	54.25±4.5	12.22±12.9	10.4±13.1	39.16±10.2
SZMC 27157	2.12±2.3	7.2±9.4	0.52±1.3	6.15±12.5	21.78±11.3	63.82±12.8
SZMC 27158	72.69±11.3	37.24±5.3	15.05±1.1	51.86±11.8	32.5±12.9	30.78±1.2
SZMC 27159	75.6±9.7	37.79±13.3	15.55±12.7	15.65±3.2	60.2±13.5	54.73±12.3
SZMC 27160	18.22±5.9	78.43±5	55.44±8.8	24.4±8.4	5.94±14.1	56.92±9.4

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27161	62.68±12.8	23.08±11.5	5.34±13.9	84.84±1.2	86.02±15.8	12.96±7.1
SZMC 27162	69.05±5.4	67.79±11.3	41.65±13.6	30.45±7	8.48±8.1	47.99±9.4
SZMC 27163	59.16±12.3	64.27±4.9	0.65±9.8	83.03±16.4	29.38±10.4	70.86±5.6
SZMC 27164	27.86±10.8	39.52±8.8	50.85±14.6	22.69±5.1	40.02±5.1	52.89±4.8
SZMC 27165	62.5±12.2	8.8±10.8	51.02±1.7	49.32±4.5	64.36±12.2	41.31±9
SZMC 27166	17.62±6.5	56.51±15.2	41.46±15.2	55.49±10.3	47.25±7.3	78.84±3.4
SZMC 27167	67.79±13.3	45.2±12.7	51.06±4.7	6.01±12.7	28.11±7.6	46.49±10.1
SZMC 27168	66.57±12.8	82.4±13.7	45.46±2.1	34.06±3.8	78.93±5.4	52.49±2.9
SZMC 27169	61.2±12.7	82.02±4.5	5.04±15.9	1.93±12.6	16.23±4.1	59.62±9
SZMC 27170	78.89±8.2	85.48±7.8	44.44±1.3	35.15±8.9	13.16±8.1	75.26±3.2
SZMC 27171	17.26±15.7	10.01±9.8	15.22±3	11.34±9.8	87.08±15.1	58.49±3.1
SZMC 27172	67.28±13.8	77.26±3.8	55.53±12.4	33.91±2.9	54.31±3.5	93.94±7.5
SZMC 27173	81.69±13.2	98.86±13.9	44.84±2.5	83.42±13.9	54.29±5.8	52.93±5.2
SZMC 27174	92.89±16.4	24.27±3.5	45.31±1.6	44.31±5.3	32.02±3.5	32.14±3.7
SZMC 27175	91.15±3.2	89.08±3.4	45.33±11.7	69.83±5.3	13.48±2.4	21.94±7.6
SZMC 27176	57.66±1.1	32.88±3.2	48.59±11.3	98.59±4.7	98.97±14.4	15.72±9.1
SZMC 27177	80.79±8.4	91.82±10.1	24.4±8.7	45.6±2.5	60.16±8	40.2±16.3
SZMC 27178	27.86±1.7	0.03±3.2	34.44±3.5	0.16±7.6	55.36±14.9	17.56±4.9
SZMC 27179	97.15±15	54.1±16.3	42.31±15.4	81.55±13.9	71.99±8.8	20.62±12

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27180	57.91±13	12.41±5.8	94.29±5.9	24.09±5.7	66.69±3.9	0.27±11.9
SZMC 27181	61.96±10	66.7±16.3	94.44±7.9	31.64±6	36.96±9.6	70.81±7.3
SZMC 27182	27.08±1.1	53.66±12.8	14±5.8	52.19±9.5	76.43±12	0.15±14.9
SZMC 27183	96.27±4.3	25.84±5.2	43.42±15.7	24.41±5.9	19.07±6.8	14.36±9
SZMC 27184	6.51±8	72.17±9.9	41.24±9.8	46.31±5.5	28.45±9.7	45.12±10.9
SZMC 27185	97.01±3.4	94.29±6.6	94.05±2.1	98.48±1.8	91.87±14.6	91.41±5.5
SZMC 27186	1.72±8	39.09±7.6	55.45±9.9	93.85±4.4	78.08±4.6	52.73±10.5
SZMC 27187	96.77±6.6	95.23±1.9	94.42±1.6	91.44±6	86.34±8.5	80.9±5.2
SZMC 27188	97.96±3.4	97.01±1.1	90±14.2	96.91±5.6	90.41±10.5	96.49±14.8
SZMC 27189	71.86±3.8	65.41±12.4	8.91±12.7	24±11.4	96.26±3.7	73.5±14.2
SZMC 27190	10.17±4.1	0.6±13.6	40.44±5.1	50.42±15.2	82.22±15.7	3.8±11.3
SZMC 27191	20.58±2.6	90.09±8.2	44.44±15	44.19±5.3	3±7.1	43.43±13.6
SZMC 27192	67.69±2.1	65.15±13.4	34.41±13.8	45.32±8.7	26.11±1.7	48.6±15.4
SZMC 27193	70.62±13	28.51±16.3	25.24±10.8	46.24±6.9	12.84±6.2	37.01±8.5
SZMC 27194	72.8±6.6	62.9±8.7	50±5.2	42.41±9.2	74.31±1.1	20.39±12.1
SZMC 27195	56.92±7.5	95.07±4.6	84.48±1.2	91.46±6.3	32.27±4.2	30.31±14
SZMC 27196	51.57±7.1	6.96±11.7	0.82±8.6	4.42±11	84.81±3.8	74.62±10.7
SZMC 27197	1.71±5.4	3.47±11.1	34.21±4.3	6.19±11.3	64.61±4.4	42.92±6.6
SZMC 27198	67.16±8.9	0.38±15.9	35.3±9.5	4.44±5.8	45.61±10	39.01±7.4

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27199	67.79±5	93.25±9.7	19.09±7.9	9.36±1.5	72.02±16.3	64.25±3.8
SZMC 27200	75.26±14.8	20.37±1.7	48.34±1.2	63.93±10.2	90.74±13.5	11.13±11.1
SZMC 27201	96.25±11.7	97.62±3.9	8.48±2	69.44±1.3	43.25±10.5	1.43±7.2
SZMC 27202	91.78±7.2	79.05±3.9	44.59±7.1	56.02±6.2	17.93±11.3	42.92±10.8
SZMC 27203	81.96±8.1	62.06±13.7	10±2.2	15.4±9.9	3.18±7	55.31±6.7
SZMC 27204	77.06±4.4	65.26±7.4	44.33±2.9	34.58±11.1	46.69±1.4	37.56±15.3
SZMC 27205	87.51±13.2	97.29±12.7	81.29±13.7	61.61±8.6	12.76±6.9	11.89±5.4
SZMC 27206	77.02±11.8	43.35±12.8	44.14±3.3	12.55±1.6	44.43±4.3	55.01±6.7
SZMC 27207	76.08±12.3	17.35±4.4	14.81±10.8	14.04±12.6	12.24±6.1	30.21±6.8
SZMC 27208	52.12±5.1	26.61±5.1	25.22±7.5	33.54±1.4	21.03±14.7	6.53±14.5
SZMC 27209	10.78±12.7	82.49±3	44.43±11.8	66.91±2.7	66.05±2.1	29.07±13.1
SZMC 27210	62.56±13.9	13.48±1.7	58.8±3	24.93±11.3	59.15±15.6	38.08±15.4
SZMC 27211	61.1±8.7	63.74±3.3	50.42±6.4	36.23±16.1	28.28±10.3	46.85±6.8
SZMC 27212	55.21±10.1	55.6±7.2	51.03±12.3	33.48±1.6	33.65±11.2	23.6±15
SZMC 27213	16.71±7.2	86.62±16.3	38.51±13.2	98.32±15.3	57.19±4.2	30.97±14.1
SZMC 27214	60.7±14.3	57.83±14.8	32.44±2.4	16.4±6.3	75.91±14.5	28.02±13.5
SZMC 27215	60.69±10.8	2.7±14.7	35.42±7.7	5.4±14.2	1.24±9.7	34.57±14.9
SZMC 27216	7.16±15.6	35.03±7.7	30.41±4.3	98.61±15.2	56.31±12.1	42.21±2.5
SZMC 27217	69.7±16.2	7.56±12.2	30.4±10.5	48.24±11.5	60.45±8.3	0.26±2.1

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27218	7.52±5.2	41.52±2	33.49±15.3	13.14±3.8	79.41±5.6	53.81±11.3
SZMC 27219	70.9±8.6	50.77±9.5	42.24±11.9	88.04±6.3	43.84±3.2	47.53±4.3
SZMC 27220	1.75±4.5	37.85±4.7	19.23±10.1	56.21±5.3	62.5±2.5	41.73±8.6
SZMC 27221	50.75±10.6	8.49±12.8	54.24±8.3	10.23±5	98.72±11.6	70.38±9.3
SZMC 27222	57.59±6.1	1.18±12	53.28±8.9	45.46±9.7	7.91±3.5	53.4±10.1
SZMC 27031	93.62±2.1	92.19±2.8	92.18.98±8.3	93.95±12.2	96.27±11.7	97.42±14.7

Table S 4. Antimicrobial effects of EFs' metabolites of *J. communis* extracted with hexane from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27149	50.71±7.2	4.15±1.5	12.12±7.3	96.26±3.6	14.62±13.5	22.51±11.6
SZMC 27150	19.43±15.4	15.79±8.5	58.03±1.5	26.2±12.6	71.74±11.8	18.41±6.5
SZMC 27151	5.49±10.8	31.93±10	56.63±13.6	45.43±12.4	77.47±1.9	24.03±13.7
SZMC 27152	70.24±6.9	55.23±2.5	46±10.8	11.55±4.9	4.48±16.3	36.95±7.6
SZMC 27153	1.37±4.8	5.2±7.8	34.84±15.7	88.32±14.8	90.13±16	9.11±12.1
SZMC 27154	41.96±5.7	29.53±12.2	62.9±6.6	51.69±12.5	38.12±4.8	37.54±3.3

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27155	0±9.7	43.12±10.9	26.44±3.5	26.52±5.1	16.68±1.2	43.11±14.1
SZMC 27156	5.67±12.1	51.94±11.7	28.95±2.7	22.45±2.9	46.67±10.7	38.85±4.5
SZMC 27157	31.95±4	33.93±7.9	24.63±7.2	21.95±13.3	37.09±13.9	51.49±13.5
SZMC 27158	52.39±1.3	43.21±12.8	18.32±1.2	22.58±6	44.94±13.7	49.86±2.4
SZMC 27159	47.25±3.8	11.35±6.5	24.45±9	22.53±8.3	77.59±1.8	52.27±5.1
SZMC 27160	7.64±5.2	42.45±4.4	8.08±2.9	23.15±15.8	71.54±6.6	32.73±11.8
SZMC 27161	45.91±14.1	53.3±15.3	62.03±8.4	92.24±1.5	17.66±6.4	34.59±4.2
SZMC 27162	20.65±2.1	42.17±9.8	44.13±16.2	64.86±2.2	39.23±9.1	98.34±13.1
SZMC 27163	48.61±10.4	37.39±9.6	52.91±6.7	8.62±13.5	21.65±12.7	22.64±2.3
SZMC 27164	75.09±15.6	3.35±12.7	20.4±8.1	25.19±1.5	83.28±9.3	37.75±15.8
SZMC 27165	13.93±3.4	49.9±16.2	40.31±15.9	22.61±15.6	31.06±5.2	37.27±2
SZMC 27166	76.08±14.4	7.11±16.3	84.44±2.7	20.94±11	49.99±1.5	20.17±5.2
SZMC 27167	95.5±11.4	35.21±5	33.84±1.7	32.51±12.3	2.06±6.1	38.47±4.3
SZMC 27168	27.29±13.8	54.54±15.7	50.95±6.5	65.24±3	44.24±13.6	44.15±11.8
SZMC 27169	21.47±5.7	44.49±3.2	35.4±8.9	18.23±14.8	12.39±10.9	21.24±2.3
SZMC 27170	20.15±9.5	54.45±10.3	1.18±3	46.55±1.4	17.92±7.1	8.83±8.6
SZMC 27171	53.78±11.1	25.45±16.3	26.14±11.8	31.29±3.3	36.84±12	46.98±3.2
SZMC 27172	47.25±1.5	53.29±11.9	46.92±5	29.6±6.2	6.23±4.9	34.99±11.4
SZMC 27173	32.65±6.1	32.08±3.1	21.94±5.9	45.69±11.2	25.76±7	44.51±15.2

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27174	30.47±1.1	51.55±10.5	42.96±13.6	4.85±13	64.94±15.5	38.87±8
SZMC 27175	43.25±6	13.2±14.5	42.45±3.4	65.06±10	17.25±9	20.12±9.3
SZMC 27176	41.11±6.1	27.75±1.1	32.41±9.8	48.86±4.3	29.18±15.6	22.41±5.3
SZMC 27177	12.96±13.7	57.35±15.4	42.32±12.3	8±8.7	33.68±12.4	40.09±9.5
SZMC 27178	47.24±9.3	57.9±5.9	85.84±12	36.11±13	26.6±6.6	48.59±3.9
SZMC 27179	48.62±7.7	15.11±5.3	51.61±2	58.04±8.4	48.8±15.8	55.89±15.5
SZMC 27180	62.68±9.1	5.73±10.5	42.44±5.9	61.25±9.6	28.55±2.7	39.36±10.5
SZMC 27181	36.86±13.3	49.5±9.2	23.43±13.5	23.32±10.5	64.67±15.4	51.6±8.9
SZMC 27182	53.45±3.4	72.71±16.1	40.4±4.8	30.3±11.5	98±7.8	30.06±7.1
SZMC 27183	35.98±5.1	0.03±6.7	0.95±11.4	26.89±9.6	97.88±2.1	19.6±7.2
SZMC 27184	39.31±5.4	47.39±2.7	31.51±12.9	42.5±7.6	9.06±5	4.87±10.7
SZMC 27185	42.01±1.8	52.49±14.9	36.42±16	46.24±2.8	32.36±10	59.18±15.7
SZMC 27186	53.13±15.4	71.25±13.9	65.4±6.5	64.26±10.9	66.44±16.2	0.98±10.2
SZMC 27187	60.37±1.2	74.54±1.6	12.14±13	33.05±8.3	93.73±2.2	35.77±1.7
SZMC 27188	30.93±7.3	47.2±4.6	23.04±2.7	44.45±7.2	55.36±4.9	42.93±8.6
SZMC 27189	27.05±7.5	77.57±3.3	30.98±3.6	22.46±3.9	22.07±12.3	76.74±14.3
SZMC 27190	4.79±3.6	47.51±5.8	54.94±15	21.4±2.7	15.61±5	44.25±13.7
SZMC 27191	0.24±10.7	44.1±10.7	50.48±11.8	43.29±12.4	45.2±4.6	9.7±9.8
SZMC 27192	53.32±12.3	54.9±14.1	34.02±15.8	38.92±1.4	44.04±3.1	45.15±12

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27193	17.91±15.3	73.17±13.4	36±6.1	35.46±14.6	17.48±6.1	28.37±9.8
SZMC 27194	27.3±7.5	45.33±3.4	34.63±14.2	56.26±7	7.46±11.3	50.52±11
SZMC 27195	25.6±14.6	53.03±15	12.94±8.5	13.6±7.5	31.42±5.7	78.47±1.3
SZMC 27196	13.42±10.6	74.01±10.2	62.42±13.7	6.35±6.6	51.52±14.1	26.64±2.1
SZMC 27197	32.29±10.1	45.17±3.3	62.05±11.3	31.02±12.7	36.57±6.9	32.44±10.7
SZMC 27198	46.14±5	15.91±13.1	50.1±7.7	10.88±10	43.2±10.8	1.03±15.2
SZMC 27199	59.91±11.1	0.4±7	26.42±3.2	0.53±8.1	16.68±15.8	47.58±5.4
SZMC 27200	8.32±3.2	13.32±4.9	31.02±7.5	59.43±3.8	41.66±8.3	56±4.6
SZMC 27201	43.31±4.2	52.11±7.8	24.44±2.8	42.2±5	21.17±6.5	44.87±11.2
SZMC 27202	3.64±2.2	49.44±15.8	53.43±9.6	13.4±9.4	61.31±6.2	36.81±13.8
SZMC 27203	11.63±8.4	53.59±10.3	36.46±5.5	22.63±6.1	66.78±9.1	73.73±8.9
SZMC 27204	15.93±15.9	14.53±7.3	4.04±14.1	85.32±10.6	28.79±5.1	9.6±5.5
SZMC 27205	32.52±15.9	9.04±3.1	58.08±11.8	29.16±9	9.25±6.1	14.58±15.2
SZMC 27206	31.27±15.1	45.44±9.6	24.9±13	25.24±3.1	46.76±6.8	5.13±1.3
SZMC 27207	46.78±8.2	34.41±4.5	84.88±4.1	86.26±13	41.15±4.7	33.38±1.1
SZMC 27208	16±10	13.97±6.1	32.18±13.1	63.89±12.6	4.26±12.6	3.06±15.8
SZMC 27209	59.75±10.4	50.71±8.8	33.46±11.1	29.1±13.6	25.9±11.2	14.9±4.7
SZMC 27210	39.36±9.2	22.94±2.3	42.8±3.2	56.3±14.7	40.1±13.5	5.25±12.9
SZMC 27211	28.48±6.6	51.52±2.1	16.62±14.7	59.83±6	44.24±10.1	57.29±4

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27212	16.66±8.2	59.34±11.3	26.04±8.3	23.6±6.2	46.22±10	44.51±11.2
SZMC 27213	95.88±10.8	32.54±5.3	48.93±14.6	23.61±9.8	2.8±11	57.85±14.9
SZMC 27214	40.53±2.4	25.5±14	44.9±6.8	26.62±9.2	14.86±7.2	86.6±5.6
SZMC 27215	45.48±6.1	35.79±14.4	38.05±5.7	19.12±7.6	39.91±2.9	53.07±11.7
SZMC 27216	14±7.2	14.15±14.9	41.92±2.5	39.4±16.4	6.28±3	45.74±12.2
SZMC 27217	9.56±8.6	52.24±4.6	12.46±12.5	39.29±15.4	38.47±2.2	4.89±3.3
SZMC 27218	34.3±15.7	14.95±7.9	18.45±12.9	32.23±8.9	26.6±1.2	45.28±15.1
SZMC 27219	67.69±11	40.05±7.5	48.12±4.9	64.1±9.1	18.32±14.8	17.46±8.4
SZMC 27220	49.34±8.8	31.77±9.3	46.05±6.3	11.14±1.8	4.18±12.8	44.45±11.6
SZMC 27221	61.97±11.9	25.95±14.4	42.64±4.2	23.44±8	6.39±4.4	58.86±9.1
SZMC 27222	41.42±14.9	25.91±10.6	34.48±12	9.13±16.3	17.99±14.5	45.06±7.1
SZMC 27031	91.84±6	84.01±4.1	6.44±7	16.61±6.7	7.85±13.5	32.64±8.7

Table S 5. Antimicrobial effects of EFs' metabolites of *J. communis* extracted with chloroform/methanol from mycelia.

Collection code	DW (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27149	178.45±11.3	1.01±1.7	77.44±9	16.53±11.7	25.85±4.8	24.73±4.4	56.3±14.4
SZMC 27150	228±3.7	41.61±15.6	59.56±5.8	49.15±8.6	51.62±11.8	37.98±3.5	86.95±2.7
SZMC 27151	163.94±10.2	83.8±15.5	58.19±10	49.1±10.3	30.88±5.1	41.31±5	68.59±2.3
SZMC 27152	222.49±2	8.77±5.8	18.35±10.1	86.52±8	47.29±9.3	45.2±7.6	54.97±10.6
SZMC 27153	198.23±11.7	34.57±8	76.18±3.3	76.51±3.1	15.6±13.5	18.39±5.1	46.96±14.7
SZMC 27154	234.67±4.3	45.98±2.8	1.22±12	81.79±6.6	44.79±3.2	20.67±10	19.13±8.9
SZMC 27155	278.45±6.5	29.68±9	95.11±13.3	99.19±5.8	71.46±6.7	65.37±2.8	52.63±5.9
SZMC 27156	298.11±8.4	57.96±6.7	87.04±1.3	91.61±7.5	10.4±6.5	39.59±13.6	98.7±9.3
SZMC 27157	214.81±8.8	29.44±9	7.2±9.4	86.33±2	21.78±7.9	85.99±14.9	1.39±10.6
SZMC 27158	167.98±3.7	53.29±12.3	37.24±5.3	42.38±5.1	32.5±14.9	46.66±8.5	24.39±12.9
SZMC 27159	293.92±8.6	55.19±5.5	37.79±13.3	77±8.6	60.2±14	15.56±11.5	58.84±9.1
SZMC 27160	285.39±4.5	33.57±10.9	78.43±5	78.67±14.9	5.94±10.7	45.9±13.2	10.61±1.7
SZMC 27161	275.51±10	9.98±2.2	23.08±11.5	81.67±9.9	86.02±8.4	82.81±10.8	70.91±6.1
SZMC 27162	330.33±6.9	7.24±2.4	67.79±11.3	49.72±13.8	8.48±2.4	47.54±14.4	64.08±14.1
SZMC 27163	228.16±15.6	36.54±15.1	64.27±4.9	32.01±2.6	29.38±16.4	18.46±11.6	58.96±1.9
SZMC 27164	316.16±5.9	81.31±3.8	89.52±8.8	94.04±3.5	90.02±15	86.53±10.7	94.38±12.2
SZMC 27165	289.32±4.6	55.33±13.3	8.8±10.8	70.76±4.2	64.36±9.9	94.26±3.1	52.85±2.6
SZMC 27166	387.12±13.1	35.12±7	56.51±15.2	77.33±14	47.25±7.7	28.39±3.3	28.85±9.7
SZMC 27167	198.56±11.7	31.51±1.6	45.2±12.7	85.8±7.6	28.11±9.7	81.22±5.9	82.69±7.8
SZMC 27168	267.34±15.2	52.92±9.8	82.4±13.7	13.36±3.7	78.93±10.1	30.2±8.7	97.9±4.7

Collection code	DW (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27169	193.25±12.3	55.65±11.7	82.02±4.5	62.23±9.5	16.23±3.1	50.93±4.1	26.7±10.7
SZMC 27170	209.12±3.7	18.79±8.8	85.48±7.8	49.28±10.4	13.16±7.3	81.96±7.3	14.82±10.4
SZMC 27171	207.16±12.6	95.15±6.9	10.01±9.8	85.39±8	87.08±10	50.54±1.6	74.29±3.9
SZMC 27172	220.45±2.6	43.39±9.8	77.26±3.8	77±2.5	54.31±8.3	43.43±11.2	52.24±5.8
SZMC 27173	298.34±4.2	13.71±8.9	98.86±13.9	29.21±2.5	54.29±5.6	69.91±14.9	41.32±3.5
SZMC 27174	192.67±9	33.1±7.8	24.27±3.5	43.38±1.4	32.02±13.8	14.35±15.6	33.81±10.8
SZMC 27175	144.66±15.8	69.92±15.8	89.08±3.4	18.16±11.9	13.48±16.3	84.94±8.1	26.64±14
SZMC 27176	288.45±3.9	64.58±9	32.88±3.2	29.09±14.8	98.97±16.2	97.05±2.8	34.38±16
SZMC 27177	298.53±14.3	61.26±9.5	91.82±10.1	68.21±4.7	60.16±1.1	83.51±1.9	43.75±2
SZMC 27178	265.43±6.5	43.59±3.2	0.03±3.2	41.67±6.8	55.36±3.4	95.67±2.6	23.42±4.8
SZMC 27179	285.45±6	65.49±13.9	54.1±16.3	70.46±11.9	71.99±9.6	21.58±7.6	0.87±2.6
SZMC 27180	299.38±1.2	60.09±8.2	12.41±5.8	55.89±9	66.69±8.6	12.03±16.1	24.8±13.6
SZMC 27181	244.32±12.5	20.17±15	66.7±16.3	5.71±14.4	36.96±11.7	62.61±7.1	53.79±11.3
SZMC 27182	187.32±3.6	25.63±11.3	53.66±12.8	14.09±2.4	76.43±15.2	71.06±8.5	51.22±4.3
SZMC 27183	199.36±12	10.36±13.3	25.84±5.2	77.8±4.1	19.07±2.9	16.43±13.1	44.53±11.4
SZMC 27184	298.34±9.8	23.74±4.4	32.17±9.9	4.92±13.1	28.45±3.1	0.29±15.5	26.86±10.2
SZMC 27185	331.45±8.8	43.44±4.1	54.29±6.6	79.51±5.2	19.87±5.1	54.24±11.7	6.06±8.3
SZMC 27186	332.45±1.5	92.4±7.3	39.09±7.6	53.77±2.8	78.08±7.6	86.87±3.9	94.41±1.9
SZMC 27187	284.45±13.2	75.32±7.6	65.23±1.9	8.98±10.5	86.34±3.5	79.54±6.7	53.95±15
SZMC 27188	256.41±11.5	1.16±15.7	71.01±1.1	30.93±11.3	60.41±9.4	46.08±11.9	61.1±3.7
SZMC 27189	276.41±5.9	58.92±3.2	65.41±12.4	93.43±2.2	66.26±5.3	44.87±5.4	76.73±3.7
SZMC 27190	233,45±1.9	8.23±1.1	0.6±13.6	7.97±7.5	82.22±5.7	82.35±15	35.24±3.1

Collection code	DW (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27191	284.34±11.1	64.5±4.9	90.09±8.2	6.16±10.5	3±1.8	80.2±9.5	16.53±11
SZMC 27192	199.23±12.1	42±7.6	65.15±13.4	11.18±1.8	26.11±5.5	3.33±7.9	25.88±12.8
SZMC 27193	176.43±7.2	48.81±4.1	28.51±16.3	80.23±5.5	12.84±3	37.27±7.9	64.21±14.4
SZMC 27194	144.56±13.3	10.3±13.5	62.9±8.7	22.37±6.5	74.31±14.6	33.22±7.1	92.59±4.1
SZMC 27195	277.36±2.2	9.2±9.8	95.07±4.6	53.45±8.3	32.27±16.3	66.14±11.6	53.54±10.3
SZMC 27196	256.34±1.2	80.4±14.8	6.96±11.7	27.52±13.8	84.81±2.6	39.44±9.1	16.08±15.8
SZMC 27197	233.45±10.7	45.35±3.8	3.47±11.1	32.35±8	64.61±5	12.93±14.6	38.59±1.9
SZMC 27198	269.34±8.4	59.94±14.3	0.38±15.9	32.98±2.4	45.61±5.4	51.49±12.7	31.82±10.5
SZMC 27199	299.41±11.7	93.18±7.3	93.25±9.7	46.54±4.2	72.02±2.9	50.66±10.8	39.63±8.2
SZMC 27200	301.36±4.7	19.89±3.5	20.37±1.7	90.11±1.9	70.74±16.1	37.03±9.6	33.34±7.5
SZMC 27201	331.85±5.6	10.24±10.1	97.62±3.9	8.57±14.1	43.25±15.8	59.39±7	3.66±6.1
SZMC 27202	249.81±11.7	28.89±8.8	79.05±3.9	61.28±12.9	17.93±8.6	71.37±10	23.87±14.4
SZMC 27203	366.12±5.2	53.56±3.2	62.06±13.7	65.15±5.7	3.18±11	29.9±1.3	28.84±7.6
SZMC 27204	341.34±13.7	6.91±7.9	65.26±7.4	83.72±8.3	46.69±15.7	9.51±15.7	60.48±11.9
SZMC 27205	112.67±9.6	3.62±6.5	97.29±12.7	92.12±1.2	12.76±10.5	56.05±2.3	50.78±3.4
SZMC 27206	288.56±6.3	19.98±12.1	43.35±12.8	72.13±3.6	44.43±3.9	61.67±4.7	37.24±16.4
SZMC 27207	298.34±8.7	29.55±10.5	17.35±4.4	8.28±16	12.24±4.9	55.66±6.9	43.14±3.6
SZMC 27208	255.34±9.7	13.5±10.5	26.61±5.1	3.61±12.8	21.03±7.5	23.95±15.2	74.6±10.3
SZMC 27209	232.67±10.2	51.55±1.4	82.49±3	78.14±13	66.05±7.8	53.59±12.7	46.44±3.4
SZMC 27210	289.34±4.6	15.55±16	13.48±1.7	49.21±2.6	59.15±11.8	34.76±15.8	43.06±9.5
SZMC 27211	189±1.5	58.9±12	63.74±3.3	13.33±15	28.28±8.5	44.95±4.1	45.5±8.2
SZMC 27212	213.66±11.9	46.52±6.2	55.6±7.2	55.78±11.6	33.65±9.5	39.51±12.9	28.95±8

Collection code	DW (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27213	219.23±3	58.15±16.3	86.62±16.3	2.41±10.2	57.19±12.5	70.24±5.9	16.84±8.5
SZMC 27214	298.33±7	19.05±6.7	57.83±14.8	92.07±8.5	75.91±14.7	41.75±13.5	11.63±5.2
SZMC 27215	272.45±2.5	48.3±12.1	2.7±14.7	31.95±14.7	1.24±9.6	74.01±10.1	39.12±3.9
SZMC 27216	276.11±13.3	28.81±14.9	35.03±7.7	80.21±4.7	66.31±1.9	33.21±7.6	95.74±14.5
SZMC 27217	324.56±5.9	54.44±2.3	7.56±12.2	45.03±5.2	60.45±4	24.5±13.3	17.75±14.2
SZMC 27218	311.9±7.1	26.16±12.3	41.52±2	45.65±15.8	79.41±8.8	59.05±9	79.99±9.5
SZMC 27219	344.23±3.5	98.42±16.4	50.77±9.5	32.87±7.4	43.84±9.4	30.31±11.2	66.52±3.5
SZMC 27220	401.89±5.8	39.41±12.8	37.85±4.7	2.42±16.2	62.5±1.4	14.5±5.8	43.9±2
SZMC 27221	228.67±10.4	28.14±7.7	8.49±12.8	92.68±13.6	68.72±4.1	12.06±5.9	4.91±8.4
SZMC 27222	321.73±9.5	44.55±5.6	1.18±12	47.41±13.1	7.91±6.5	20.88±13.3	37.2±15.7
SZMC 27031	382.12±8.56	84.99±3.8	92.19±2.8	79.41±7.9	56.27±10.3	63.98±7.9	82.5±4.6

Table S 6. Antimicrobial effects of EFs' metabolites of *A. asiatica* extracted with chloroform from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27067	54.26±15	5.79±12.8	22.32±6.1	24.21±15.1	22.32±11.3	24.21±2.6
SZMC 27068	53.35±9	25.54±4.3	3.76±6.1	94.32±13.3	3.76±7.9	24.32±14
SZMC 27069	72.25±1.1	97.55±7.6	24.59±8	53.59±4.7	24.59±15.7	53.52±12.1

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27070	92.18±15.8	90.33±2.6	87.35±13.5	37.27±7.4	87.35±14.1	37.27±5.5
SZMC 27071	63.18±7.7	33.85±8.8	8.41±2.9	34.59±5.9	8.41±3.9	34.52±8.9
SZMC 27072	63.95±4.1	84.11±15.2	69.08±7.5	55.64±6.9	69.08±15.5	55.64±6.9
SZMC 27073	32.59±3.2	87.45±11.5	32.01±4.6	45.47±11.7	32.01±15.3	45.47±5.9
SZMC 27074	27.52±15.6	38.71±8.1	30.06±15.9	74.47±14	30.06±4.1	74.47±1.3
SZMC 27075	70.06±15.4	71.55±13.4	58.02±15.8	77.14±3.9	58.02±8	77.14±8.2
SZMC 27076	35.94±6.5	84.79±11.9	5.59±10.7	44.6±9.4	5.59±12.5	44.6±4.8
SZMC 27077	96.41±14.2	91.54±10.2	62.08±8.9	75.19±8.1	62.08±11.2	75.12±16
SZMC 27078	92.34±11.2	44.35±9.8	48.87±4.2	43.59±9.4	48.87±5.3	43.52±2.9
SZMC 27079	98.14±2.3	90.54±16.4	69.53±6.3	93.45±6.8	69.53±15	23.45±1.5
SZMC 27080	1.55±12	90.27±3.9	34.38±3.3	91.26±4.8	34.38±12.7	21.26±11.8
SZMC 27081	49.7±12.4	74.46±8.9	26.42±14.3	97.37±2.6	26.42±12	27.37±8.6
SZMC 27082	93.23±7.6	78.14±2.2	33.79±16	30.45±5.3	33.79±12.6	30.45±8.3
SZMC 27083	80.54±16	64.56±16.3	43.41±5.9	50.42±8.7	43.41±14.9	50.42±13.1
SZMC 27084	34.51±15.7	7.2±15.5	28.48±3.9	56.46±9.3	28.48±9.6	56.46±8.5
SZMC 27085	21.38±1.5	5.62±9.6	8.56±2.6	24.69±3.9	8.56±10.4	24.62±11.7
SZMC 27086	66.55±5.9	40.73±5.6	53.84±6.5	34±7.9	53.84±12.9	34±15.4
SZMC 27087	76.62±16.2	45.67±16.2	19.14±10.8	25.73±7.9	19.14±10	25.73±5
SZMC 27088	6.6±9.8	83.98±12.5	27.3±15.8	56.39±9.5	27.3±16.1	56.32±9

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27089	89.99±16.10	62.78±3.4	40.3±11.2	74.45±12	40.3±8.6	74.45±1.7
SZMC 27090	19.64±13.2	82.88±3.8	17.11±15.9	25.34±3.5	17.11±7.6	25.34±15.3
SZMC 27091	93.52±12.4	0.68±14.9	12.25±13.6	56.53±11.8	12.25±13.2	56.53±2.5
SZMC 27092	61.92±8.2	75.42±4.6	75.35±1.2	54.02±6.5	75.35±12.7	54.02±8.3
SZMC 27093	3.79±5.6	48.15±6.4	26.86±11.7	13.44±13.9	26.86±9.8	13.44±12
SZMC 27094	77.68±8.5	80.42±5.1	30.17±2.5	59.24±2.6	30.17±14.4	52.24±7.4
SZMC 27095	18.52±5.8	38.27±13.2	1.54±2.9	23.9±7.2	1.54±11	23.2±1.6
SZMC 27096	45.36±7.4	49.04±6.7	45.99±15.3	40.21±10.3	45.99±9.5	40.21±13.4
SZMC 27097	5.63±5.2	29.88±15.1	24.89±2.4	39.11±9.6	24.89±13.8	32.11±6.8
SZMC 27098	82.78±3.7	96.35±8.4	28.04±7.1	46.14±8.2	28.04±8.2	46.14±16.1
SZMC 27099	38±3.2	17.73±10	97.09±8.2	12±9.8	97.09±10.3	12±5.4
SZMC 27100	5.53±6.2	20.94±12.4	0.55±8	37.3±10.3	0.55±6.1	37.3±16.3
SZMC 27101	54.89±1.5	24.58±9.3	24.92±15.7	16.54±1.6	24.92±7	16.54±2.3
SZMC 27102	69.76±13.9	90.93±2.8	67.91±2.4	75.41±6.5	17.91±5.8	75.41±13.5
SZMC 27103	40.14±14.6	60.48±4.4	15.24±16	90.54±15.4	15.24±4.4	20.54±10.8
SZMC 27104	80.82±8	92.41±11.8	2.01±13.8	73±14.4	2.01±10.3	73±8.6
SZMC 27105	2.93±11.8	36.88±15.9	24.14±8.2	14.22±4.2	34.14±14.9	14.22±1.9
SZMC 27106	14.55±16.3	51.72±16.3	28.53±9.3	72.64±2.5	28.53±7.9	72.64±3.6
SZMC 27107	78.86±8.4	91.34±12.8	14.8±13.1	43.49±5.7	14.8±13.2	43.42±10.1

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27108	53.17±5.9	92.47±2.2	22.89±5.1	5.4±15.7	22.89±8.1	5.4±10.3
SZMC 27109	47.2±1.6	98.11±12.7	46.79±12.6	94.42±14.7	46.79±5.5	24.42±10
SZMC 27110	28.21±1.3	4.93±5.7	18.1±12.8	93.73±5.4	18.1±1.4	23.73±3.7
SZMC 27111	24.36±13.5	37.05±10.9	32.8±1.7	29.3±7.1	32.8±3.3	22.3±10.3
SZMC 27112	24.49±10.6	57.86±12.6	55.63±11.7	46.35±4.5	55.63±6.3	46.35±6
SZMC 27113	22.21±15.1	14.44±10.2	13.14±15.8	37.41±2.6	13.14±11.6	37.41±15
SZMC 27114	34.19±4.3	2.29±4.6	34.4±12.3	42.63±7.2	34.4±7.6	42.63±2.3
SZMC 27115	88.14±16.4	87.89±13.8	4.98±7	72.46±12.5	4.98±7.9	72.46±1.2
SZMC 27116	47.7±2.6	16.54±6.5	58.83±12.4	32.12±14.8	58.83±3.6	32.12±7.2
SZMC 27117	51.72±2.4	11.84±2.4	5.62±2.7	46.71±2	5.62±4.3	46.71±13.1
SZMC 27118	63.11±2.3	92.88±14.9	38.41±3.4	1.34±5.8	38.41±2	1.34±3.7
SZMC 27119	57.37±9.7	58.77±10.8	18.51±10.9	67.32±15.2	18.51±15.8	67.32±5.8
SZMC 27120	55.03±16.2	93.39±6.1	29.84±14.3	44.63±14.9	29.84±9.7	44.63±10.5
SZMC 27121	34.11±2.8	98.66±7.8	57.85±4.8	47.4±15.9	57.85±15.3	47.4±14.8
SZMC 27122	26.49±4	94.2±8.8	1.84±8.6	14.53±15.6	1.84±3.8	14.53±16.2
SZMC 27123	22.01±8.5	49.39±2.9	50.2±16.1	36.39±8.6	50.2±12.3	36.32±9.9
SZMC 27124	91.67±2.9	0.73±6.5	36.19±7.2	41.39±6.2	36.19±12.7	41.32±15
SZMC 27125	9.33±9.6	33.54±15	36.23±1.2	33.52±3.3	36.23±10.4	33.52±1.5
SZMC 27126	49.73±4	98.17±14.3	92.26±5	46.56±13.2	92.26±14.8	46.56±15.6

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27127	31.08±10.6	96.41±15.2	17.76±16.1	15.61±3.3	17.76±1.5	15.61±6.5
SZMC 27128	66.91±3.6	41.64±11.3	36.58±3.3	24.47±15.3	36.58±8	24.47±14.7
SZMC 27129	38.94±8.8	78±13.3	9.14±6	67.44±8.4	9.14±2.3	67.44±8.5
SZMC 27130	14.3±14	95.3±5.9	49.61±4.9	79.6±14	49.61±2.7	72.6±8.3
SZMC 27131	10.25±13.3	34.64±1.6	50.94±11.8	90.61±15.2	50.94±2.6	20.61±7.7
SZMC 27132	45.26±2.5	92.75±15.3	50.02±11.2	25.34±15.7	50.02±10	25.34±10.2
SZMC 27133	76.87±14.8	91.65±2	58.27±4	42.36±14	58.27±3.4	42.36±15.8
SZMC 27134	9.19±9.5	17.87±6.7	24.48±4.8	73.62±5.2	24.48±7.4	73.62±3.3
SZMC 27135	95.26±11.7	12.9±4.7	56±12.5	75.34±11.5	56±16.1	75.34±1.4
SZMC 27136	28.2±6.5	30.65±1.6	5.45±9.5	54.4±14	5.45±10.8	54.4±14.7
SZMC 27137	92.02±8.8	71.21±1.1	51.73±14.8	34.46±12.3	51.73±10.3	34.46±14.4
SZMC 27138	97.53±5.7	8.42±16	13.01±14.4	65.33±13.1	13.01±13.5	65.33±4.3
SZMC 27139	56.05±9.7	55.16±12	9.85±2.1	35.71±11.1	9.85±15.7	35.71±4.9
SZMC 27140	17.03±2.9	86.78±4.4	18.13±6.4	27.19±6.1	18.13±16.4	27.12±8.8
SZMC 27141	30.96±14	1.4±1.4	41.8±9.1	75.66±4.9	41.8±5.5	25.66±5
SZMC 27142	25.43±14.1	50.15±13.4	79.37±11.4	11.45±1.2	79.37±11.4	11.45±5.1
SZMC 27143	77.9±1.3	60.14±11.6	41.01±10.3	13.52±11.1	41.01±10.3	13.52±9.7
SZMC 27144	93.48±11.3	62.15±15.4	26.78±1.8	46.55±13.9	26.78±4.2	46.55±9.7
SZMC 27145	91.01±15.4	0.43±5.4	79.23±3	7.17±12.8	79.23±16.2	7.17±3.9

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27146	6.95±11.2	61.49±11.4	94.66±6.4	21.42±2.3	94.66±13.2	21.42±4.4
SZMC 27147	62.12±9.9	5.27±14.1	72.46±3.1	0.54±5.3	72.46±1.1	0.54±3.7
SZMC 27148	20.98±14.6	11.72±9.1	21.27±10.6	42.14±2.9	21.27±10.7	42.14±15.6

Table S 7. Antimicrobial effects of EFs' metabolites of *A. asiatica* extracted with ethyl acetate from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27067	34.36±5.6	21.84±7.4	8.25±2.7	3.11±2.9	8.25±12.6	3.11±5
SZMC 27068	18.43±10.3	9.53±2.4	6.65±15.1	49.43±8.2	6.65±4.6	49.43±4.4
SZMC 27069	90.24±10.9	80.99±15.4	51.03±14	54.34±15.9	51.03±16	54.34±9.3
SZMC 27070	84.98±8.9	91.77±13.7	71.08±7.7	39.55±12.4	71.08±13.9	39.55±12.4
SZMC 27071	74.28±14.7	92.48±9.4	5.81±9.3	94.9±12.5	5.81±14	94.9±4.5
SZMC 27072	48.22±2.3	87.46±6.1	89.14±11.8	59.49±11.8	89.14±10.5	59.49±5.3
SZMC 27073	77.84±7.6	6.45±1.7	25.3±3	51.26±1.5	25.3±1.6	51.26±2.6
SZMC 27074	82.43±15.7	36±2.7	43.29±15.1	5.53±2.9	43.29±14.1	5.53±13.3
SZMC 27075	65.46±4.8	25.02±10.2	10.23±16.1	39.45±5.9	10.23±6.8	39.45±4.3

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27076	74.97±10.7	72.48±3.3	95.3±15.8	17.11±12.6	95.3±1.1	17.11±1.1
SZMC 27077	96.65±13.2	90.6±14.7	93.06±16	12.52±8.4	93.06±5.2	12.52±10.7
SZMC 27078	93.42±4.9	76.87±1.3	43.91±10.9	41.25±14.6	43.91±11.3	41.25±11.2
SZMC 27079	74.19±1.3	92.64±8.1	20.32±5.5	21.52±10.3	20.32±5.5	21.52±11.6
SZMC 27080	41.44±6.7	97.82±14.4	47.83±3.5	32.66±4.2	47.83±14.6	32.66±6.1
SZMC 27081	91.84±4.6	52.62±1.5	83.65±10.2	6.44±14	83.65±5.6	6.44±13.7
SZMC 27082	94.45±5.1	78.73±5.9	76.98±11.7	50.73±5.3	76.98±4.6	50.73±3.9
SZMC 27083	50.2±11.9	36.27±4.4	67.36±9.3	21.61±15.3	67.36±14.2	21.61±8
SZMC 27084	1.94±8.6	78.87±7.2	32.04±9.1	94.95±14.3	32.04±14.6	94.95±15.5
SZMC 27085	53.07±15.8	53.87±4.4	52.29±2.1	16.7±12.5	52.29±14.8	16.7±1.6
SZMC 27086	97.42±13.1	25.35±8.8	4.45±11.7	32.32±1.6	4.45±12.9	32.32±10
SZMC 27087	72.49±12.1	10.95±6.4	89.78±10.8	94.57±9.5	89.78±1.8	94.57±16.2
SZMC 27088	35.32±7.5	94.96±8.2	53.96±3.5	64.54±10.1	53.96±2.6	64.54±4.6
SZMC 27089	22.8±13.50	53.9±11.5	28.3±13.2	39.22±8.4	28.3±5.8	39.22±7.6
SZMC 27090	81.32±5.7	95.57±9.3	24.2±11.3	14.05±5.8	24.2±2.3	14.05±12.9
SZMC 27091	87.31±12.7	33.27±5.2	80.31±11.6	52.36±12.9	80.31±2	52.36±2.1
SZMC 27092	52.66±13.3	2.15±8.5	84.31±6.5	4.69±13.8	84.31±5.6	4.69±11.6
SZMC 27093	35.31±16.3	92.12±16.3	32.54±12.1	37.92±8.6	32.54±9.7	37.92±15
SZMC 27094	11.75±9.2	91.02±7.2	44.43±14.2	11.35±8.9	44.43±12	11.35±9.8

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27095	3.1±4.9	67.75±6.7	81.23±7.9	63.95±4.4	81.23±9.8	63.95±2.8
SZMC 27096	92.64±5.8	58.76±9.3	64.55±9.2	34.04±4.4	64.55±2.9	34.04±11.8
SZMC 27097	72.54±5	66.57±5.9	1.3±5.2	34.05±11.9	1.3±14.9	34.05±3.8
SZMC 27098	61.71±15.7	97.31±2.6	26.42±13.8	30.34±2.1	26.42±16.2	30.34±1.6
SZMC 27099	50.45±12.7	65.95±4.5	80.78±16.3	52.59±9.3	80.78±6	52.59±5.1
SZMC 27100	87.78±13.5	36.97±4.1	79.74±6.7	9.37±13.1	79.74±12.2	9.37±15.3
SZMC 27101	78.04±13.3	93.1±14	7.15±12.7	4.33±8.9	7.15±11	4.33±9.1
SZMC 27102	81.35±14.5	92.81±14.7	65.27±3.9	90.02±13.9	65.27±8.3	90.02±9
SZMC 27103	77.99±5.3	15.69±14.5	68.33±16.2	47.09±12.4	68.33±12.8	47.09±6.8
SZMC 27104	90.72±11.7	89.14±10.9	49.44±4.1	14.34±3.3	49.44±4.8	14.34±12.5
SZMC 27105	87.94±3.4	4.41±10.7	41.28±3.4	53.55±15.6	41.28±11	53.55±12.3
SZMC 27106	49.91±13	10.69±3.3	8.75±6.6	22.22±1.6	8.75±1.1	22.22±4.6
SZMC 27107	11.1±12.8	53.6±12.4	28.49±2.6	22.76±6.6	28.49±1.9	22.76±11.3
SZMC 27108	45.38±4.9	14.22±9.9	45.63±3	69.46±1.6	45.63±12.4	69.46±12.4
SZMC 27109	3.4±8.9	99.43±12	44.36±8.6	75.32±7.1	44.36±15.6	75.32±10.2
SZMC 27110	76.14±15.5	37.68±5.9	95.78±3.8	21.31±7.6	95.78±15.3	21.31±10.8
SZMC 27111	91.07±6.5	87.49±11.8	35.86±8	43.41±3.4	35.86±3	43.41±13.1
SZMC 27112	82.85±5.5	80.15±8.8	89.89±10.5	45.66±4.3	89.89±14.4	45.66±12.6
SZMC 27113	37.94±13.6	13.42±10	82.5±15.7	0.95±3.9	82.5±6.8	0.95±5.6

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27114	10.9±12	78.27±9.6	68.37±15.7	43.35±12.5	68.37±6.3	43.35±14.9
SZMC 27115	78.89±8	23.29±16.3	71.07±7.7	63.74±14.7	71.07±15.9	63.74±6.5
SZMC 27116	28.4±7.3	13.05±11.1	26.31±10.3	42.64±2.7	26.31±8.9	42.64±13.6
SZMC 27117	64.81±7.2	73.94±16	55.46±2.5	56.14±4.5	55.46±7.1	56.14±9.4
SZMC 27118	49.17±6.9	38.9±4.4	31.36±4.6	32.56±9.3	31.36±6.9	32.56±8.4
SZMC 27119	40.3±13.2	44.97±6.1	12.67±8.3	4.04±8.4	12.67±8.4	4.04±5.8
SZMC 27120	94.21±9	62.5±16.1	54.26±11.7	33.95±14.8	54.26±3.9	33.95±8.8
SZMC 27121	68.24±2.8	27.39±13.7	13.25±6	29.17±7	13.25±10.2	29.17±16.1
SZMC 27122	93.99±15.2	18.57±15.9	40.7±8.4	97.42±1.5	40.7±10.7	97.42±8.2
SZMC 27123	80.55±9.3	95.27±10.2	51.12±9.1	34.26±2	51.12±1.8	34.26±2.2
SZMC 27124	74.4±16.2	69.93±10.8	13.96±3.6	59.6±13.9	13.96±14.1	59.6±1.8
SZMC 27125	97.25±4	80.49±7.2	43.62±3.3	51.52±13.9	43.62±13.4	51.52±15.1
SZMC 27126	95.08±15.7	36.51±3.4	8.03±1.8	54.43±8.3	8.03±2.5	54.43±8.4
SZMC 27127	94.99±11.3	75±14	18.72±10.6	24.16±13.5	18.72±5.7	24.16±4.4
SZMC 27128	79.54±5.4	52.95±9	30.63±13.7	4.59±11.6	30.63±8.5	4.59±11.8
SZMC 27129	26.35±15.9	68.68±13.5	13.46±6.6	3.01±9.7	13.46±4.3	3.01±15.4
SZMC 27130	20.25±6.5	17.08±11.8	24.58±8	14.66±7.7	24.58±9.7	14.66±7.5
SZMC 27131	0.53±10.6	74.94±15.3	57.1±2.2	43.44±3	57.1±5.8	43.44±10.1
SZMC 27132	57.88±12.2	64.71±6.8	2.72±13.5	74.93±10.2	2.72±14.2	74.93±14

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27133	73.97±16.2	71.44±10.8	24.7±13	54.44±7.2	24.7±4.7	54.44±15.9
SZMC 27134	68.4±16.4	98.72±13.9	6.12±7.5	17.44±13.3	6.12±13.9	17.44±1.6
SZMC 27135	96.78±5.7	11.33±2.7	19.78±9.7	31.73±16.2	19.78±15.2	31.73±2.7
SZMC 27136	71.59±11.9	38.06±10.6	26.01±12.3	49.69±1.2	26.01±13.6	49.69±3.2
SZMC 27137	93.11±15.1	95.59±1.7	42.02±1.3	35.47±4.8	12.02±9.4	35.47±14.6
SZMC 27138	93.66±3.7	45.86±7.5	80.63±15.4	25.64±8.1	80.63±10.3	25.64±16
SZMC 27139	97.52±3.7	93.33±8.9	40.21±8	24.44±14.6	40.21±4.2	24.44±15.9
SZMC 27140	70.94±4.3	37.19±10.3	59.69±13.9	12.7±1.5	59.69±6	12.7±3.3
SZMC 27141	68.78±4.3	43±7.5	43.79±14.9	42.51±9.5	43.79±11.2	42.51±7.5
SZMC 27142	70.77±13.7	7.02±11.6	37.73±16.1	10.7±8.5	37.73±10.4	10.7±8.4
SZMC 27143	93.89±10.7	26.57±9	27.33±5.4	5.36±5.9	27.33±13.5	5.36±4.5
SZMC 27144	99.28±12.8	40.38±2.5	6.98±4.7	77.44±2.2	6.98±13.5	77.44±14.7
SZMC 27145	96.58±11.7	25.4±5.2	37.75±11.1	31.07±10.9	37.75±12.3	31.07±14.6
SZMC 27146	25.68±6.6	69.06±4.5	32.32±10.1	44.99±2.7	32.32±4.9	44.99±14.4
SZMC 27147	72.45±2.9	63.38±10.2	54.28±2.8	49.56±13.6	54.28±12.1	49.56±9
SZMC 27148	90.18±8.6	91.18±14.3	21.56±6.9	44.05±9.9	21.56±5.5	44.05±13.3

Table S 8. Antimicrobial effects of EFs' metabolites of *A. asiatica* extracted with hexane from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27067	2.24±14.6	89.15±6.2	25.25±15.9	43.38±1.3	25.25±6.3	43.38±2.2
SZMC 27068	17.27±15.8	38.25±2.8	30.06±6.6	30.3±12.5	30.06±9.8	30.3±9.6
SZMC 27069	22.25±14.1	68.4±14.2	11.9±10.4	33.38±13.4	11.9±8.4	33.38±15.8
SZMC 27070	0.66±9.1	59.81±5.4	48.91±15.4	54.03±4.3	48.91±15.7	54.03±6.2
SZMC 27071	82.25±11	76.15±13.7	15.24±5.4	35.84±7.5	15.24±14.5	35.84±9.8
SZMC 27072	28.68±6.5	40.05±14.2	25.13±4	34.33±11.1	25.13±13.9	34.33±16.3
SZMC 27073	76.11±13.8	7.11±2.9	20.84±12.8	53.03±7.4	20.84±8.4	53.03±15.7
SZMC 27074	68.75±14.4	72.37±15.2	31.07±5	34.55±5.2	31.07±5.6	34.55±3.3
SZMC 27075	31.59±9.2	10.3±14.1	33.05±2.2	24.32±15	33.05±14.4	24.32±7.9
SZMC 27076	29.49±11.2	89.1±12.2	66.13±14.3	33.34±12.7	66.13±1.4	33.34±3.7
SZMC 27077	47.85±9	11.57±15.2	28.81±13.5	33.52±14.9	28.81±2.3	33.52±13.6
SZMC 27078	19.31±14	5.68±2.5	42.86±13.3	34.54±8.2	42.86±11.1	34.54±12.7
SZMC 27079	45.43±11	24.15±7.6	61.87±2.2	37.38±15.3	61.87±9.4	37.38±9.2
SZMC 27080	26.18±5.5	31.87±5.2	56.8±11.1	87±13.2	56.8±16.3	87±8.4
SZMC 27081	1.13±9.4	31.9±8.8	30.47±9.1	43.8±10.2	30.47±7.7	43.8±6.1
SZMC 27082	32.41±15	16.05±6	28.16±16.1	53.72±16.1	28.16±14.3	53.72±9.5
SZMC 27083	42.25±5.2	25.09±2.9	18.15±2.9	25.33±5.4	18.15±16.4	25.33±5.5

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27084	25.06±3.5	54.76±13.7	2.35±6.4	53.27±3.9	2.35±12.9	53.27±2.5
SZMC 27085	16.33±13.9	23.55±2.7	47.16±5.1	41.53±14.2	47.16±7.1	41.53±4
SZMC 27086	54.92±13.5	11.33±4	49.21±11.4	53.75±5	49.21±1.4	53.75±7.7
SZMC 27087	32.25±9.2	25.09±5.4	10.32±4.9	22.43±9.4	10.32±7.2	22.43±12.6
SZMC 27088	46.57±10	16.03±7.3	51.8±5.2	13.02±14.1	51.8±1.8	13.02±4.1
SZMC 27089	26.07±14.90	38.09±6.10	56.44±4.7	2.81±14.2	56.44±3.6	2.81±12.5
SZMC 27090	47.41±15.7	44.28±3.8	68.02±12	23.05±11.5	68.02±5.4	23.05±13.3
SZMC 27091	71.94±6.3	16.02±4.8	82.52±16	13.22±16.3	82.52±1.3	13.22±13.8
SZMC 27092	0±9.4	4.12±1.6	27.31±10.8	31.85±14.8	27.31±7.2	31.85±15.8
SZMC 27093	41.38±2.8	32.57±2.7	59.21±1.7	27.33±2.6	59.21±3.9	27.33±15.7
SZMC 27094	53.58±2.4	82.29±14.6	11.28±4.6	35.04±12.9	11.28±12.5	35.04±3.3
SZMC 27095	84.79±4.4	59.96±8.5	16.82±16.1	58.34±4.4	16.82±8.3	58.34±16.3
SZMC 27096	61.23±6.8	39.29±2.4	7.16±4.5	13.53±11	7.16±4.4	13.53±15.3
SZMC 27097	53.34±16.1	34.9±5.2	59.49±2.7	33.82±8.9	59.49±5.6	33.82±2.2
SZMC 27098	96.01±7.4	57.92±5.1	43.25±6.8	23.83±6.4	43.25±10.1	23.83±15.2
SZMC 27099	54.8±5.7	46.36±8.9	28.02±6.4	11.82±13.9	28.02±8.1	11.82±11.4
SZMC 27100	17.48±3.7	14.8±14.3	28.85±14	32.84±16.2	28.85±3.7	32.84±3.6
SZMC 27101	11.31±13.6	84.35±13.1	18.77±11.9	17.02±7.2	18.77±10.9	17.02±5.3
SZMC 27102	49.61±12.3	45.79±14.5	56.14±9.2	34.18±4.9	56.14±14.2	34.18±6.2

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27103	25.79±1.7	57.57±11.4	26.31±5	30.38±13.2	26.31±3.2	30.38±3.5
SZMC 27104	15.63±8.9	27.12±14.3	46.46±6.1	15.22±8.5	46.46±6	15.22±4
SZMC 27105	40.37±15.5	8.17±15.3	38.13±10.4	53.51±5	38.13±4.1	53.51±2.3
SZMC 27106	30.18±13.4	1.03±5.2	15.8±13.6	23.24±14.1	15.8±2.4	23.24±6.1
SZMC 27107	90.44±1.9	48.99±13.5	5.29±1.5	30.1±5.3	5.29±9.4	30.1±9.2
SZMC 27108	34.58±6.8	41.83±4.6	7.53±14.4	14.39±10.3	7.53±12.1	14.39±3.6
SZMC 27109	51.48±10.2	71.86±4.8	28.71±6.4	33.44±14.8	28.71±6.2	33.44±12.7
SZMC 27110	14.18±8.3	33.55±6.7	94.71±1.7	19.01±5.2	94.71±3.5	19.01±15.1
SZMC 27111	26.99±8	52.24±13.2	3.17±1.1	70.32±15.6	3.17±8.6	70.32±14.4
SZMC 27112	81.96±12	47.78±10.9	28.77±9	12.33±16.3	28.77±11.3	12.33±12.2
SZMC 27113	27.46±8.7	21.45±16.4	4.4±3.1	18.33±12.6	4.4±15	18.33±9.6
SZMC 27114	38.13±5.5	16.06±12.1	53.98±3.9	25.41±5	53.98±12.9	25.41±14.1
SZMC 27115	86.89±13.2	11.35±5.8	21.66±16.2	48.33±1.5	21.66±7.9	48.33±10.2
SZMC 27116	43.07±7.6	27.91±5.6	97.5±11	39.35±8.7	97.5±1.9	39.35±4.7
SZMC 27117	73.57±13.7	36.09±1.5	22.79±9.3	33.81±6.1	22.79±8	33.81±2.8
SZMC 27118	21.54±5.1	58.22±3.5	9.73±1.3	31.13±2	9.73±15.8	31.13±13.6
SZMC 27119	52.02±14.3	89.04±1.7	13.35±4.6	9.13±13.6	13.35±15.3	9.13±14.6
SZMC 27120	30.57±4.2	36.47±3	38.49±12.2	12.44±9.9	38.49±15.7	12.44±10.3
SZMC 27121	9.64±8.4	26.24±7.3	2.26±15.7	79.57±13.4	2.26±8.7	79.57±14.1

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27122	29.3±9	27.67±9.2	46.27±2.8	39.2±12.2	46.27±11.7	39.2±5.4
SZMC 27123	69.54±5.7	6.56±6.9	26.65±5.3	57.34±14.3	26.65±12.5	57.34±5.4
SZMC 27124	15.23±13.8	56.36±13.6	8.54±6	38.08±10.4	8.54±2.2	38.08±7.2
SZMC 27125	41.32±7.5	17.81±14.1	28.66±4	43.91±6.7	28.66±7.4	43.91±7.9
SZMC 27126	49.31±2.7	11.65±7.1	24.98±15.9	33.34±3.3	24.98±6.7	33.34±9.7
SZMC 27127	35.32±16	17.47±15.1	7.03±4.5	53.33±5.6	7.03±3.2	53.33±11
SZMC 27128	23.71±6.3	12.72±3.3	22.58±9.3	24.13±9.1	22.58±12.5	24.13±2.6
SZMC 27129	68.44±2.8	31.59±1.8	31.21±8.1	20.21±10.7	31.21±13.4	20.21±1.5
SZMC 27130	23.07±15.5	24.61±9	35.02±13.5	47.51±12.5	35.02±7.9	47.51±14.7
SZMC 27131	27.04±12.8	56.29±14.3	48.62±4.2	42.55±15.1	48.62±4.8	42.55±12.8
SZMC 27132	15.11±3.4	38.92±2.2	34.27±15.6	73.15±15.9	34.27±12.7	73.15±9.8
SZMC 27133	68.78±13	66.15±5.8	11.99±9.5	23.14±5.6	11.99±14.3	23.14±3.2
SZMC 27134	39.37±9.2	41.77±6.3	34.91±3.1	51.95±9.5	34.91±5.6	51.95±3.2
SZMC 27135	28.57±8.4	26.99±1.1	20.59±12.9	34.87±5.7	20.59±6.4	34.87±15.7
SZMC 27136	37.25±1.3	6.62±8.2	27.2±2.3	52.23±1.7	27.2±10	52.23±7.3
SZMC 27137	74.86±7.2	77.6±8.9	86.89±6.2	83.93±7.3	56.89±6.7	33.93±2.4
SZMC 27138	22.06±3.1	64.75±7.2	37.27±6.2	47.52±15.4	37.27±12.2	47.52±6.2
SZMC 27139	44.23±15.1	45.13±15.1	32±12.4	33.38±12.9	32±11.2	33.38±8.6
SZMC 27140	46.81±6.4	32.53±15.1	48.44±5.1	28.93±2	48.44±3.3	28.93±5.7

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27141	49.77±7.8	46.45±1.7	23.68±12.6	52.19±3.9	23.68±2.5	52.19±16.2
SZMC 27142	32.2±15.9	32.09±12.5	48.71±6.8	37.97±8.4	48.71±10.1	37.97±1.8
SZMC 27143	15.97±14.1	52.79±8.5	20.82±5.1	44.07±15	20.82±11.1	44.07±4.3
SZMC 27144	16.81±2.4	29.28±9.6	47.64±10.8	33.32±13.2	47.64±6.1	33.32±7.8
SZMC 27145	82.28±11.8	4.45±5.2	20.38±2.3	4.28±3.4	20.38±8.9	4.28±13.4
SZMC 27146	38.64±9.5	15.26±14.5	37.15±7.9	39.88±13.6	37.15±2.8	39.88±9.3
SZMC 27147	76.93±5.1	18.28±6.1	26.52±11.2	11.58±3.6	26.52±3.2	11.58±3
SZMC 27148	58.17±11.7	58.51±8.2	37.92±9.5	3.35±3.6	37.92±7.1	3.35±5.4

Table S 9. Antimicrobial effects of EFs' metabolites of *A. asiatica* extracted with chloroform/methanol from mycelia.

Collection code	Dry weight (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27067	302.22±10.6	75.94±8.5	34.95±13.3	3.22±11.7	70.79±1.8	3.22±16.4	70.79±9.7
SZMC 27068	235.02±2.7	74.63±1.2	53.61±12.9	28.74±12.3	43.7±13	28.74±7.5	43.7±5.7
SZMC 27069	302.53±5.7	69±7.7	33.88±7.4	7.32±15.2	91.41±2.3	7.32±1.1	91.41±3.5
SZMC 27070	262.52±5	90.87±11.4	83.66±12.6	8.24±11.5	94.22±14.2	8.24±14.6	94.22±4.8
SZMC 27071	225.63±13.3	68.51±13.2	33.38±14.9	24.14±4.8	13.21±2.7	24.14±2.9	13.21±3.8

Collection code	Dry weight (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27072	103.24±5.5	6.04±3.7	27.92±14.1	5.05±8.6	13.43±7	5.05±4.5	13.43±4.5
SZMC 27073	343.12±10.3	64.04±7.5	58.43±12.2	4.62±5.9	54.32±4.1	4.62±16	54.32±8
SZMC 27074	24.32±3.3	18.46±10.5	32.22±4.4	46.74±2.5	37.41±9.6	46.74±2.6	37.41±1.1
SZMC 27075	224.23±11	60±4.4	8.63±2.4	74.88±3.3	14.67±5.6	74.88±7.2	14.67±10.6
SZMC 27076	246.34±8.3	39.32±8.2	55.54±12.6	37.85±13.3	24.4±15.3	37.85±6.7	24.4±15.9
SZMC 27077	142.33±9.3	63.79±11.6	35.6±15.1	27.74±14.3	54.61±6.9	27.74±14.8	54.61±4.3
SZMC 27078	333.17±5.9	76.21±4.3	56.67±1.9	68.18±15.5	33.95±2.1	68.18±11.8	33.95±8.7
SZMC 27079	423.23±9.2	86.69±12	25.69±14.7	46.97±9.7	44.33±14.8	46.97±9.8	44.33±1.4
SZMC 27080	342.12±16.3	53.27±7.2	88.41±3	99.3±6.1	17.44±15.4	99.3±10.5	17.44±1.3
SZMC 27081	262.12±6.2	52.19±12.8	13.4±4.1	55.63±15.5	30.94±3.6	55.63±12.5	30.94±6
SZMC 27082	321.31±10.9	65.31±13.5	6.88±9.4	30.99±7.5	52.13±11.5	30.99±3	52.13±13.8
SZMC 27083	665.22±6.7	64±3.1	6.1±12.3	66.24±6.5	60.53±6.9	66.24±7.3	60.53±10.2
SZMC 27084	250.22±14.9	47.35±8.5	35.68±4.4	31.97±12.4	6.42±9.9	31.97±14	56.42±7.5
SZMC 27085	45.26±3	74.22±9.2	56.36±11	34.3±2.5	47.43±8.2	34.3±15.8	47.43±9.9
SZMC 27086	134.23±9.9	92.42±12	51.6±11.6	42.59±1.3	30.06±2	42.59±11	30.06±8.5
SZMC 27087	324.32±14.5	72.72±3.6	88.49±3	70.68±2	19.49±14.2	70.68±11.9	19.49±4.6
SZMC 27088	364.02±15.8	12.65±12.9	92.26±8.4	33.74±8.9	11.22±2.6	33.74±15.1	11.22±2.9
SZMC 27089	202.15±1.8	97.01±10.8	94.05±7	56.48±12.6	66.46±9.5	56.48±7	66.46±3.6
SZMC 27090	322.32±13.5	0	49.72±1.5	16.95±14	57±13.7	16.95±7.6	57±3.8
SZMC 27091	222.22±1.7	56.03±10.6	4.65±6.4	21.72±4.8	24.17±1.9	21.72±12.7	24.17±15.5
SZMC 27092	201.14±12.8	15.62±3.2	85.26±12.1	70.13±13.3	13.39±14.9	70.13±2.6	13.39±9.1
SZMC 27093	103.05±12.2	92.92±7.6	76.53±2.2	36.54±1.6	92.4±14.8	36.54±2.6	92.4±16
		13.61±8.4					

Collection code	Dry weight (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27094	435.22±7.4	93.46±4	3.89±4.2	55.3±16.4	44.06±8.6	55.3±14.9	44.06±15.5
SZMC 27095	225.25±14.5	58.73±14.3	30.93±2.8	69.93±13.1	10.34±10.9	69.93±12.1	10.34±8.3
SZMC 27096	560.66±9.9	90.86±16	1.64±9.9	24.8±2.3	93.51±8.3	24.8±11.3	93.51±1.9
SZMC 27097	245.33±8.4	62.18±15.6	45.35±6.1	21.1±7.8	5.39±14.2	21.1±7.1	5.39±5.6
SZMC 27098	322.2±12.4	82.3±10.5	3.86±10.8	5.08±10.8	3.61±1.7	5.08±13.1	3.61±15.7
SZMC 27099	234.02±11.9	96.71±8.4	74.42±4.5	44.22±8.9	14.42±13.8	44.22±13.6	14.42±13
SZMC 27100	222.22±10.9	18.03±3.3	71.88±5.7	89.16±12.1	60.41±5.7	89.16±6.9	0.41±15.9
SZMC 27101	622.32±8.5	23.73±8.1	16.6±12	35.29±13.1	94.17±6.8	35.29±8.2	94.17±7.8
SZMC 27102	63.62±3.3	78.39±15.6	60.25±16.3	74.7±6.7	55.29±7.1	64.7±11.3	55.29±12.5
SZMC 27103	233.31±13.6	47.68±14.8	53.9±4.3	3.97±10.3	96.12±11.8	3.97±9.6	96.12±15
SZMC 27104	156.24±10	79.84±8.6	36.85±8.5	47.36±10.6	4.36±14.4	47.36±2.4	4.36±7.9
SZMC 27105	110.62±15.8	48.94±4.7	9.39±9.3	48.43±15.5	41.79±7.4	48.43±15.3	41.79±13.1
SZMC 27106	222.22±2.7	0.18±14.3	10.99±9.1	73.6±11.4	94.16±11.3	73.6±8.4	94.16±13.3
SZMC 27107	622.21±3	60.57±12.3	77.85±10.3	0.19±14.7	71.33±12.8	0.19±11.8	71.33±3.8
SZMC 27108	336.54±11.4	2.27±1.1	51.43±10.4	15.98±6.8	44.12±9.7	15.98±14	44.12±8.8
SZMC 27109	20.13±12.9	29.04±13.9	1.15±5.9	50.28±7.6	20.22±8.3	50.28±11.4	20.22±7.7
SZMC 27110	252.44±12.7	14.55±7.3	50.36±3.2	44.25±14.3	47.64±7.9	44.25±7.1	47.64±1.4
SZMC 27111	226.23±9.5	31.27±13.6	9.94±1.3	37.23±5.5	2.22±1.2	37.23±7.5	52.22±8.4
SZMC 27112	203.2±10.4	36.32±1.9	49.86±7.6	22.89±4.4	27.39±1.8	22.89±10.5	27.39±2.7
SZMC 27113	225.22±1.8	33.75±11	62.22±2.2	54.95±14	64.7±2.9	54.95±14.3	64.7±7.9
SZMC 27114	363.23±3	17.67±7.3	0.57±2.3	60.6±12.4	94.43±9	60.6±9.6	94.43±12.5
SZMC 27115	452.35±5.8	36.19±13.4	6.2±9.2	29.13±3.3	19.05±3.3	29.13±11.5	19.05±6.5

Collection code	Dry weight (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27116	325.24±5.5	73.25±10.2	93.33±11.4	38.12±5.9	55.01±6.8	38.12±4.9	55.01±11
SZMC 27117	234.15±8	36.2±12.1	97.08±3.6	12.41±16.4	13.43±7.3	12.41±4.9	13.43±13
SZMC 27118	246.34±6.1	20.91±13.1	96.85±10.5	8.41±9.2	4.97±12.1	8.41±16	4.97±6.1
SZMC 27119	165.33±6.2	52.61±12.5	30.92±5.2	30.89±8.3	41.9±9.7	30.89±9.5	41.9±12.8
SZMC 27120	420.26±11.7	87.8±4.5	22.57±1.8	82.08±10.6	62.47±14	82.08±1.3	12.47±10
SZMC 27121	335.64±10.1	55.89±5.5	77.07±11.1	38.41±5.9	74.95±13.7	38.41±2	4.95±14.4
SZMC 27122	142.04±13.2	52.57±15.8	73.08±12.5	14.77±4.5	6.44±8.7	14.77±16.3	6.44±7.2
SZMC 27123	362.33±7.6	20.38±8.2	97.29±14.5	32.27±3.6	97.71±7.7	32.27±7.1	97.71±4.8
SZMC 27124	222.22±15.6	62.97±12.8	98.63±12.7	32.47±3.2	34.57±7.6	32.47±3.4	34.57±3
SZMC 27125	221.52±11.8	20.99±12.9	97.05±7	39.21±6.8	17.67±12.7	39.21±8.5	17.67±13.6
SZMC 27126	362.25±6.8	59.62±14.8	15.23±8.2	86.4±3.6	94.11±11.3	56.4±8.6	4.11±1.5
SZMC 27127	252.1±2.8	52.2±11.6	54.27±2.5	42.6±4.7	70.79±12.7	42.6±11.1	70.79±5.9
SZMC 27128	135.22±1.3	35.31±5.2	40.59±10.7	42.08±3.1	22.95±6.8	42.08±11.6	22.95±3.1
SZMC 27129	622.34±15.6	3.1±5.8	45.07±5.5	28.46±7.5	44.23±6.6	28.46±12.8	44.23±14.2
SZMC 27130	452.02±5.3	50.58±5.8	35.11±3.9	57.9±12.1	33.52±5.1	57.9±4.9	33.52±16.1
SZMC 27131	223±11.9	27.78±15.4	92.49±13.5	37.41±8.1	3±2.8	37.41±4.5	3±14.1
SZMC 27132	240.54±3.5	66.43±8.9	55.49±14.6	19.76±10.4	47.74±8.4	19.76±6.2	47.74±16.3
SZMC 27133	326.16±8.8	82.58±10.5	21.72±9.8	20.32±5.9	4.57±10.4	20.32±7.8	4.57±10
SZMC 27134	56.2±11.8	97.42±14.7	3.13±8.1	36.44±3.7	35.46±9.8	36.44±13.2	35.46±14.2
SZMC 27135	306.14±5.1	71.29±14.8	16.01±6.4	33.24±8.1	40.64±12.3	33.24±5.7	40.64±8.1
SZMC 27136	322.34±7.8	25.88±13.7	31.3±5.4	11.17±12.1	12.34±7.3	11.17±11.4	12.34±9.5
SZMC 27137	242.42±16.4	97±1.2	63.22±8.9	23.62±1.2	95.65±15.6	23.62±6.7	55.65±5.5

Collection code	Dry weight (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27138	623.32±3.5	73.64±2.4	18.8±6.1	91.97±13.8	40.21±13.7	91.97±16.4	40.21±5
SZMC 27139	212.06±7.3	32±5.2	4.69±1.2	13.38±8.1	93.04±2.6	13.38±12.1	23.04±8.5
SZMC 27140	220.12±1.5	73.63±1.8	6.78±1.6	44.62±3.4	0.29±12.4	44.62±4.2	0.29±15.1
SZMC 27141	242.34±1.4	63.29±11.4	46.51±14.5	4.22±12.1	5.73±10.4	4.22±4.6	5.73±4.4
SZMC 27142	20.35±13.2	15.83±13.8	97.14±2.7	42.9±1.1	71.46±6	42.9±6.6	21.46±1.7
SZMC 27143	44.23±2.1	63.86±5.6	42.33±2.8	8.08±1.2	42.02±2.3	8.08±4.5	42.02±8.8
SZMC 27144	646.11±4.7	93.72±12.7	28.42±2	40.48±13.1	64.52±9.9	40.48±13.6	24.52±7
SZMC 27145	254.15±13.2	65.98±2.1	2.92±15	29.6±8.3	44.92±12	29.6±7.6	44.92±2.2
SZMC 27146	124.25±1.7	98.66±9.1	17.74±8.8	34.45±3.5	4.04±9.3	34.45±11.9	4.04±3.4
SZMC 27147	623.23±10.2	90.06±1.6	74.93±13.8	49.14±4.7	27.46±15.8	49.14±2.1	27.46±6.3
SZMC 27148	12.33±13.2	57.78±12.5	28.63±10.6	40.98±7.5	34.45±1.1	40.98±1.7	34.45±5.5

Table S 10. Antimicrobial effects of EFs' metabolites of mosses extracted with chloroform from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27223	44.92±12.8	56.02±15.8	0.24±10.2	62.83±7.9	0.78±3.4	20.12±10
SZMC 27224	57.65±11	83.68±10.2	95.13±9.2	92.69±5.2	45.54±8	53.02±4
SZMC 27225	69.73±1.4	82.49±2.4	72.58±10.9	33.66±4.5	43.34±4.3	12.27±1.6
SZMC 27226	19.43±8.3	17.91±4.3	82.31±16.4	40.25±9.4	50.42±12.1	52.51±15.7

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27227	34.11±9.1	83.81±7.2	97.47±8.2	65.13±3.4	34.12±14.5	3.25±1.4
SZMC 27228	92.29±6.6	93.37±9.4	45.67±7.4	38.61±8.1	43.27±11.2	42.43±11.6
SZMC 27229	75.34±13	32.22±3.4	57.25±5.4	62.45±15.5	23.44±13.3	32.12±7.4
SZMC 27230	35.77±15.9	62.86±8.8	48.37±6	27.06±7.6	41.08±3.4	24.34±10.3
SZMC 27231	72.32±7.9	45.29±9.7	95.57±15.4	10.21±7.4	40.45±4.2	4.12±9.2
SZMC 27232	55.35±3.4	60.5±9.1	56.82±1.4	31.57±12.3	56.53±13.5	35.02±1.1
SZMC 27233	90.08±13.5	85.46±14.3	41.77±4.8	23.95±13.5	47.51±13	1.15±6
SZMC 27234	24.34±11.5	52.97±9	7.49±11.6	77.61±16	11.24±16.2	23.44±13.7
SZMC 27235	68.6±6.9	35.68±10.3	47.79±2.6	14.94±10.4	70.04±9.4	47±11.1
SZMC 27236	4.7±15.8	18.02±2.9	44.57±2.6	75.01±16	62.73±13.2	44.42±6.1
SZMC 27237	97.65±6.8	13.34±6.2	43.35±5.5	48.53±9.1	85.67±4.8	52.81±3.8
SZMC 27238	60.07±13.8	4±1.2	2.62±5.9	20.51±3.3	54.24±5.7	10.83±9.9
SZMC 27239	35.23±11.7	8.22±4.6	11.46±15.4	54.84±4	20.77±12.4	2.77±14.7
SZMC 27240	44.4±10.1	53.88±6.9	48.29±11.7	23.88±16.4	13.15±8.4	35.4±3.7
SZMC 27241	3.2±1.3	9.05±11.2	7.08±14	25.09±1.6	14.31±7.6	70.22±1.2
SZMC 27242	89.02±8.5	89.71±14.4	2.81±10.3	32.09±13.2	40.18±5.2	4.71±6.5
SZMC 27243	68.9±2.2	33.61±5.4	51.82±4.6	7.61±6.9	52.14±7.2	35.41±5.9
SZMC 27244	60.89±12.6	68.33±8	27.79±11.4	20.02±8.8	38.42±15.6	44.28±12.2
SZMC 27245	64.85±9.5	93.97±12.9	93.09±13.9	64.92±7.7	24.47±6.9	30.44±14.1

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27246	5.25±10.7	56.58±1.9	80.13±3.3	5.91±11.6	45.84±12.2	78.4±1.3
SZMC 27247	29.1±13.7	0.28±4	3.86±8.8	25.52±11.1	11.33±11	12.22±6.3
SZMC 27248	93.37±6.9	82.36±1.1	13.58±2.9	4.09±1.7	42.02±5.8	18.44±12.2
SZMC 27249	88.28±15.5	79.35±8.7	12.27±5.6	93.15±4.7	37.47±11.8	20.07±13.8
SZMC 27250	9.36±7.8	66.51±13.8	52.37±9	88.76±15.8	53.66±3.4	23.23±1.8
SZMC 27251	87.64±8.1	22.71±14.2	39.44±9.2	26.05±11.4	41.25±14.2	32.35±14.6
SZMC 27252	20.07±14.4	23.48±6.2	1.21±9	25.65±10.5	53.18±7.5	44.24±13
SZMC 27253	79.88±9.6	37.03±8.5	69.6±3.3	61.59±6.9	57.83±2.2	34.48±7.4
SZMC 27254	9.28±13.1	29.49±15.2	37.47±6	24.06±5	32.45±13.4	54.32±12.7
SZMC 27255	34.07±4.8	29.79±13	14.24±9	34.92±16	60.12±14	33.23±9.7
SZMC 27256	33.4±14	95.74±15.9	38.73±1.7	32.08±3.4	42.04±8.7	54.74±13.4
SZMC 27257	61.89±11.5	33.13±9.1	63.3±13.5	30.96±8.5	44.45±11.1	42.83±8.4
SZMC 27258	11.13±12.4	68.41±6.1	24.29±12.9	44.14±12.7	41.82±12.4	11.43±6.9
SZMC 27259	74.13±5.7	45.22±13.1	44.31±2.4	14.14±14	17.82±6.7	48.4±12.8
SZMC 27260	73.91±7.3	68.22±8.6	75.63±5.6	32.52±2.4	70.12±11.6	24.3±13.2
SZMC 27261	33.62±16.4	27.28±13.3	42.55±7.3	22.3±2	28.47±3.4	34.43±10.6
SZMC 27262	31.39±11	27.29±10.5	74.74±2.1	69.2±9.8	16.82±12.2	38.42±11.5

Table S 11. Antimicrobial effects of EFs' metabolites of mosses extracted with ethyl acetate from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27223	97.89±1.3	68.65±4.3	8.7±7.1	4.96±6.7	40.13±6.4	44.8±16.2
SZMC 27224	85.29±7.2	26.99±16.2	55.39±11.7	21.96±12.5	43.77±4.5	24.7±6.9
SZMC 27225	51.75±12.1	85.04±15.4	96.51±1.6	39.67±4.7	87.4±1.8	20.12±1.3
SZMC 27226	27.94±13.4	94.12±4.4	40.93±15.2	87.55±8.7	44.88±7.5	0.2±9.4
SZMC 27227	63.27±2.6	50.18±3.2	13.79±8.5	77.45±5.4	27.87±6.9	27.44±12.4
SZMC 27228	98.33±6.4	23.02±1.2	8.23±8.2	93.13±7.8	43.84±5.5	35.27±8.7
SZMC 27229	27.35±10.5	76.77±2	16.1±4	37.26±11.6	74.83±15.5	24.18±16
SZMC 27230	58.15±8.6	90.24±5.1	40.47±16.1	18.46±13.9	18.14±6.1	28.23±12.5
SZMC 27231	22.67±9.5	37.44±11.2	50.11±13.9	36.33±3	30.3±5.5	15.04±15.6
SZMC 27232	74.08±11.6	4.15±4	51.99±4.5	1.7±2.9	30.44±8.9	91.74±15.8
SZMC 27233	33.85±10.7	44.43±14.9	29.26±6.3	56.12±12.4	24.34±6.2	11.74±3.1
SZMC 27234	89.54±8.8	19.24±12.5	47.99±6.9	58.59±7.3	12.01±7.7	1.17±3.1
SZMC 27235	62.54±8.4	13.25±3	97.46±3	83.85±7.5	53.74±9.3	53.44±14.5
SZMC 27236	20.64±13.5	30.86±11.3	51.37±5.4	96.93±10.4	44.87±5.7	40.54±1.9
SZMC 27237	32.41±4.6	71.26±10.2	29.96±7	42.6±9.2	48.54±6	42.24±11.7
SZMC 27238	3.43±14.9	9.11±11.8	68.15±1.6	84.71±4	2.37±13.7	40.41±2
SZMC 27239	34.58±10.4	13.89±10.8	64.02±6.3	48.81±12.1	34.57±6.2	56.87±11.6

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27240	90.85±1.3	36.62±6.9	8.92±14.9	51.6±10.6	35.04±8.7	46.45±12.6
SZMC 27241	92.39±14.4	58.36±4.9	29.08±11	40.05±6	61.83±10.4	92.25±3.4
SZMC 27242	62.29±2.6	66.84±8	5.66±9	83.32±6.9	66.26±14.1	75.11±16.4
SZMC 27243	13.26±14.8	80.02±15.2	64.02±12.6	18.94±10.5	41.34±9.5	74.73±4.9
SZMC 27244	53.93±10.2	94.58±12.5	36.34±11.8	50.07±5.6	78.37±4.6	44.3±1.7
SZMC 27245	52.17±10.7	79.22±4.1	67.69±5.7	76.65±15.1	36.51±14.6	43.24±13.9
SZMC 27246	90.68±14.3	59.05±6.1	65.92±6.1	21.01±7.9	48.63±2.9	30.48±5.9
SZMC 27247	53.53±5.5	53.01±15.6	66.13±3.5	88.22±13.7	60.05±6	22.26±2
SZMC 27248	20.38±15.3	38.79±8.7	23.84±7.6	28.93±5.6	34.1±6.1	44.82±14.1
SZMC 27249	61.09±10.9	17.08±11.7	13.25±8.2	35.55±3.4	31.63±9.9	95.83±15.5
SZMC 27250	73.3±16.3	84.71±14.9	31.93±14.3	30.39±15.6	34.38±14	24.71±13.3
SZMC 27251	96.05±11	81.15±8.1	77.39±1.2	9.47±16	41.5±2.4	47.3±4.7
SZMC 27252	28.62±3.5	5.17±10.3	98.85±15	50.72±3	21.71±6.8	44.03±1.3
SZMC 27253	19.82±16.1	23.6±12.2	36.71±10.8	65.09±9.2	12.22±6.3	46.62±9.9
SZMC 27254	34.9±16.2	90.81±10.9	58.56±8.8	39.83±3.5	17.43±8.1	43.22±14.3
SZMC 27255	32.01±6.5	57.74±13.4	66.71±11.2	49.18±10.1	91.24±15.7	27.46±9
SZMC 27256	24.44±6.2	81±14	87.38±14.7	74.57±8.1	30.76±15	36.06±14.5
SZMC 27257	94.09±5.7	87.28±16.4	97.12±2	81.6±9.5	37.26±13.5	4.46±2.5
SZMC 27258	1.04±16	13.63±14.5	91.67±16.4	56.7±12.8	43.22±7.7	90.46±10.9

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27259	35.27±1.4	45.9±1.2	96.51±5.1	14.8±6.8	50.88±2.5	41.66±3.2
SZMC 27260	23.17±9.3	7.64±4.6	18.63±13.8	82.8±13.8	27.83±8	23.16±2.5
SZMC 27261	15.89±2.4	53.8±12.9	44.42±15.6	80.36±8.2	54.27±12.5	41.65±8.7
SZMC 27262	35.38±1.8	79.27±1.4	15.83±4.4	17.39±11.5	93.84±15.2	25.26±7.5

Table S 12. Antimicrobial effects of EFs' metabolites of mosses extracted with hexane from ferment broth.

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27223	52.32±8.8	38.95±10.7	4.23±5.2	92.09±3.9	15.13±6	4.34±6.8
SZMC 27224	48.22±8.9	31±13.2	8.25±16.1	35.47±4.4	45.45±13.1	41.74±10.9
SZMC 27225	39.59±7.1	94.56±5.4	10.39±7.3	76.59±10.3	24±6.6	40.37±4.3
SZMC 27226	48.41±8.5	50.08±9.1	81.6±2.3	13.12±11.6	0.62±11.2	22.14±9.9
SZMC 27227	12.13±13.2	77.36±15.7	75.6±6.9	22.82±4.1	45.54±15.8	36.17±3.8
SZMC 27228	71.8±10.4	27.69±4.3	9.8±12.6	72±11.3	30.58±5	14.56±13.3
SZMC 27229	76.2±16	69.52±2.5	55.64±14.9	0.37±13.2	40.1±13	64.1±9
SZMC 27230	49.38±12.6	98.09±5.8	50.25±1.2	85.7±2.9	24.41±5.9	15.04±6.4

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27231	24.18±14.1	54.03±10.1	69.76±15.6	57.33±14.8	57.05±6.7	84.75±16.4
SZMC 27232	60.16±3.7	89.03±13.7	21.87±5.7	21.95±9.6	43.44±16.3	48.7±4.6
SZMC 27233	30.33±2.2	66.17±12.5	2.33±2.3	60.4±8.1	22.77±10.2	42.74±1.3
SZMC 27234	3.3±4.7	63.76±12.9	26.12±3.7	41.49±12.2	53.02±6.5	45.44±4.5
SZMC 27235	37.72±4	27.05±13.4	80.3±12.6	33.65±10.1	0.07±4.2	50.75±10.1
SZMC 27236	8.31±3.4	25.55±12.4	91.22±1.9	14.14±11.4	21.83±11.7	2.34±9.1
SZMC 27237	94.04±7.7	48.9±3.8	51.19±12.9	89.43±1.4	43.42±13.3	3.33±7.9
SZMC 27238	18.42±8	15.31±15.6	35.83±4.1	73.79±5.2	44.83±7.5	12.66±8.5
SZMC 27239	73.49±9	59.08±4.3	89.65±13.8	21.24±16.2	47.54±8.4	26.5±11.5
SZMC 27240	85±11.2	14.84±1.1	32.56±13	11.32±2.8	2.83±9.7	54.8±8.7
SZMC 27241	68.88±11.6	3.25±6.9	6.64±6.8	57.63±1.8	43.68±13.2	44.54±12.7
SZMC 27242	49.28±11.8	59.4±5.3	62.77±9.7	77.22±6.1	36.74±7.7	57.76±2.6
SZMC 27243	32.38±12.3	10±8.9	23.68±8.4	98.99±5.6	13.03±12.5	23.24±9.4
SZMC 27244	66±2	22.16±16.2	71.82±6.9	15.15±6.5	36.37±16.2	12.61±15.4
SZMC 27245	43.39±7.5	62.79±6.4	15.19±4.6	18.13±2.5	24.27±11	8.26±4.5
SZMC 27246	78.05±12.5	37.61±12.4	24.17±2	21.23±10.8	14.43±5.9	36.44±4.7
SZMC 27247	35.5±15.7	94.68±7	88.89±3.4	93.46±16	55.24±14.8	4.73±14
SZMC 27248	17.43±2.8	65±5.8	64.82±9.2	44.89±7.8	47.04±9.8	24.4±14.1
SZMC 27249	16.15±4	84.29±6.6	55.4±16.4	68.11±5.2	32.64±14.5	1.11±8.3

Collection code	Inhibition rates (%)					
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27250	12.78±8.9	34.18±4.9	73.92±14.8	34.26±4.9	27.28±8.2	5.52±4.4
SZMC 27251	82.23±6.4	87.65±12.2	91.55±5.8	23.84±10.9	10.8±10.5	31.41±4.4
SZMC 27252	45.68±16.1	51.1±8	80.55±11.6	38.95±12.5	8.43±1.8	16.52±12.1
SZMC 27253	28.31±1.8	72.3±7.3	57.62±5.3	32.64±4.8	23.6±1.5	31±4.5
SZMC 27254	69.94±2.1	13.6±8.2	24.55±5.5	84.35±5.3	36.25±9.8	42.34±4.7
SZMC 27255	33.63±3	96.74±15	72.61±2.5	98.84±5.7	28.68±1.3	3.51±8.5
SZMC 27256	30.07±13.3	6.88±12.9	37.32±8.3	91.45±3.4	53.54±15.9	25.15±16
SZMC 27257	78.13±9.2	81.56±7.4	50.61±8.3	1.96±14.1	37.14±13.4	17.88±15.1
SZMC 27258	53.71±1.4	61.13±6.2	75.34±5	77.8±2.8	58.41±5.8	35.46±1.7
SZMC 27259	36.6±11.4	5.58±13.3	88.55±10.5	45.32±16.3	44.73±8.4	53.44±10.3
SZMC 27260	24.3±6	45.99±12.8	5.68±16.1	41.21±10.9	27.72±7.3	32.72±1.2
SZMC 27261	44±7	68.48±10.4	80.06±13.5	85.92±6.5	27.41±14	27.1±10.9
SZMC 27262	43.17±7.4	90.36±12.4	69.4±2.6	95.21±9.2	43.61±10.5	10.18±13.1

Table S 13. Antimicrobial effects of EFs' metabolites of mosses extracted with chloroform/methanol from mycelia.

Collection code	DW (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27223	221.23±14	40.71±5	27.55±11.5	83.13±10.1	39.1±14	0.15±10.6	21.88±4.8
SZMC 27224	242.05±14.5	35.38±7.2	19.75±7.2	42.37±14.9	19.22±16.4	23.43±3.7	58.04±7.4
SZMC 27225	323.22±12.7	19.27±10	33.68±4.3	18.82±15.2	77.36±4.3	12.33±9.1	32.47±11
SZMC 27226	198.35±4	83±11.6	36.02±2.5	35.13±7.1	13.65±12.6	24.35±4.3	43.18±7.5
SZMC 27227	202.6±3	24.23±7.9	50.36±9.3	66.95±13	13.8±4.2	14.84±13.1	28.21±9.9
SZMC 27228	265.43±16.4	89.78±5.8	18.72±12.9	93.72±2.3	1.18±14.5	75.04±8	33.75±10.6
SZMC 27229	124.04±7.3	62.97±5.9	10.21±12.8	83.83±10.9	91.55±13.8	47.85±5.2	32.85±7.6
SZMC 27230	230.01±11.3	17.95±7.3	42.16±7.1	95.26±16	90.48±8.3	40.15±5.3	41.72±8.7
SZMC 27231	261.26±12.1	2.98±11.6	41±6.3	85.89±12.3	82.74±8.2	44.87±14	12.42±9.1
SZMC 27232	232.1±7.2	47.83±1.1	87.96±14	43.69±9	12.73±6.1	36.6±14.8	25.03±6
SZMC 27233	244.31±11	59.8±10.2	95.86±9	98.63±2.1	92.02±3	43.42±7.3	51.45±13.3
SZMC 27234	212.3±2.3	4±16	80.65±16.3	56.11±2.6	38.49±7.8	75.73±6.8	13.28±12.2
SZMC 27235	324.64±5.9	31.15±5.9	4.86±6.6	12.37±11.1	77.22±5.4	11.42±2.2	43.4±12.9
SZMC 27236	330.61±6.5	19.99±7.4	53.62±16.3	21.36±9	95.66±6.4	32.55±9	0.74±3.9
SZMC 27237	211.32±3.9	89.24±13	72.69±15.5	0.06±4	59.87±1.9	45.71±15.4	50.43±4.5
SZMC 27238	255.65±12	45.86±3.8	29.76±15.4	40.88±15.7	11.55±11.8	60.15±12.5	27.57±15.2
SZMC 27239	226.01±7.7	44.02±8.6	66.97±2.4	90.63±6.7	36.24±8.4	27.44±2	38.47±9
SZMC 27240	220.6±16.1	2.65±12.2	18.1±14.6	59.76±6.2	21.33±2.6	18.04±16.1	85.21±6.5
SZMC 27241	232.23±11.8	16.97±1.5	95.94±11.6	39.03±5.6	90.35±16.4	57.22±2.4	41.33±11.4
SZMC 27242	233.44±2.7	40.25±14.8	29.75±1.3	38.42±10	26.61±11.3	56.57±5	0.73±12.5

Collection code	DW (mg)	Inhibition rates (%)					
		B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. krusei*
SZMC 27243	201.51±6.4	96.36±13.4	87.07±7.7	37.95±6	46.74±2.1	90.66±9.5	12.35±9.1
SZMC 27244	309.16±3.9	44.51±2.3	14.8±9.1	62.81±7.3	93.94±12.4	27.41±13.7	23.32±3.3
SZMC 27245	365.21±11.6	57.05±14.2	9.01±14.7	81.15±7.8	85.82±7.5	6.55±10.7	4.25±4.7
SZMC 27246	262.55±11.9	78.53±3.3	45.58±15.3	59.39±9.3	24.85±5.2	16.83±2	41.44±15.6
SZMC 27247	981.31±15	28.04±15	90.91±3.1	1.92±12.5	49.74±6.1	52.22±9.2	72.74±3.6
SZMC 27248	10.72±13.6	14.19±3.4	53.75±13.3	3.68±10.2	79.44±15.7	33.14±11	23.73±2.3
SZMC 27249	338.82±8.1	20.89±12.1	68.47±6.4	39.22±9.8	20.15±4.5	77.34±14.6	54.88±5.2
SZMC 27250	348.21±6.4	1.42±2.3	60.61±16.4	57.85±5.5	15.92±3.8	8.01±3.1	14.53±14.7
SZMC 27251	274.39±15.1	83.07±2.7	83.14±4.3	17.1±11	46.43±5.7	18.58±5	25.05±3.6
SZMC 27252	237.14±6.5	93.39±14.2	43.01±13.6	11.77±11.8	69.47±2.9	95.06±7.8	2.44±9.5
SZMC 27253	635.12±10.3	48.43±5.3	88.38±10.7	44.74±4.7	76.74±14.2	58.41±2.2	40.73±13.8
SZMC 27254	753.15±12.9	5.77±6.4	29.38±2.2	14.89±11.9	25.88±1.2	48.56±8.6	62.43±14.4
SZMC 27255	276.99±3.7	29.96±7.9	92.44±5	87.4±3.3	3.51±2.3	34.5±1.1	10.22±7.3
SZMC 27256	308.91±15.4	33.71±8.4	64.3±11.1	66.38±11.5	73.71±10.1	48.03±6.6	2.5±16.1
SZMC 27257	356.77±7.1	64.12±1.1	61.02±3.5	38.27±11.4	52.9±7.5	10.03±8.5	40.27±14.4
SZMC 27258	368.17±5.4	40.32±2.1	93.17±9	84.81±11.7	31.24±3.4	54.32±13.7	7.28±7.7
SZMC 27259	387.72±7.4	50.15±15.9	5.61±5.9	29.76±14.9	16.47±11.3	38.14±16.2	31.23±4.5
SZMC 27260	321.78±14.9	71.91±11	71.65±9.4	91.78±10.4	9.84±2.9	26.6±12.1	34.25±8
SZMC 27261	226.99±3.8	50.73±6.3	52.13±13.6	38.67±10	69.2±7.4	10.37±15.7	50.27±15.7
SZMC 27262	363.52±16.1	64.62±15.8	21.21±4.7	50.62±4.5	86.26±7.8	3.47±3.4	1.44±4.5

Table S 14. List of the EF extracts showing inhibitory activities against plant pathogenic fungi (C:M-chloroform: MeOH (4:1) extract of mycelia).

Collection code	Plant	*F. culmorum*				*R. solani*			
		Hexane	**$CHCl_3$**	**EtOAc**	**Mycelia (C:M)**	**Hexane**	**$CHCl_3$**	**EtOAc**	**Mycelia (C:M)**
SZMC 27132	*A. asiatica*	-	-	-	-	-	+	-	++
SZMC 27133	*A. asiatica*	-	-	-	-	-	-	-	+
SZMC 27134	*A. asiatica*	-	-	-	-	-	+	-	+
SZMC 27135	*A. asiatica*	-	-	-	-	-	-	-	+
SZMC 27136	*A. asiatica*	-	-	+	-	-	-	-	+
SZMC 27137	*A. asiatica*	-	-	-	+	-	-	-	++
SZMC 27138	*A. asiatica*	-	-	-	+	-	-	-	-
SZMC 27141	*A. asiatica*	-	-	-	-	-	+	-	+++
SZMC 27198	*J. communis*	-	-	-		-	-	-	+
SZMC 27206	*J. communis*	-	-	-	+	-	-	++	-
SZMC 27209	*J. communis*	-	-	-	+	-	-	-	-
SZMC 27210	*J. communis*	-	-	-	-	-	-	-	+
SZMC	*J.*	-	-	-	-	-	-	-	+

Collection code	Plant	*F. culmorum*				*R. solani*			
		Hexane	$CHCl_3$	EtOAc	Mycelia (C:M)	Hexane	$CHCl_3$	EtOAc	Mycelia (C:M)
27211	*communis*								
SZMC 27212	*J. communis*	-	-	-	+	-	-	-	+++
SZMC 27213	*J. communis*	-	-	-	-	-	-	-	+
SZMC 27214	*J. communis*	-	-	-	-	-	-	+	-
SZMC 27215	*J. communis*	-	-	-	-	-	-	+	++
SZMC 27216	*J. communis*	-	-	-	-	-	-	-	+
SZMC 27218	*J. communis*	-	-	-	-	-	-	-	+++
SZMC 27228	*Mosses*	-	-	-	-	-	-	-	+++
SZMC 27232	*Mosses*	-	-	-	-	-	-	-	++
SZMC 27233	*Mosses*	-	-	-	-	-	+	-	-
SZMC 27236	*Mosses*	-	-	-	-	-	+	-	-
SZMC 27242	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27244	*Mosses*	-	-	-	-	-	+	+	-
SZMC 27245	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27247	*Mosses*	-	-	-	-	-	-	-	++
SZMC 27250	*Mosses*	-	-	-	-	-	-	-	+++
SZMC	*Mosses*	-	-	-	-	-	-	-	+++

Collection code	Plant	*F. culmorum*				*R. solani*			
		Hexane	**$CHCl_3$**	**EtOAc**	**Mycelia (C:M)**	**Hexane**	**$CHCl_3$**	**EtOAc**	**Mycelia (C:M)**
27251									
SZMC 27252	*Mosses*	-	-	-	-	-	-	-	++
SZMC 27254	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27255	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27256	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27257	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27258	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27259	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27260	*Mosses*	-	-	-	-	-	-	-	+
SZMC 27261	*Mosses*	-	-	-	-	-	-	-	+++

Table S 15. List of the ex-type and reference strains as well as the outgroup strain (Woudenberg et al 2013) used to phylogenetic analysis of host metabolite producer *Alternaria* strains.

[1]T: ex-type strain; R: representative strain; O: outgroup

Species name	Status[1]	Genbank (ITS)	Genbank (RPB2)	Genbank (TEF1)	Host / Substrate	Country
A. alternata	T	AF347031.1	KC584375	KC584634	*Arachis hypogaea*	India
A. anigozanthi	T	KC584180	KC584376	KC584635	*Anigozanthus* sp.	Australia
A. arborescens	T	AF347033	KC584377	KC584636	*Lycopersicon esculentum*	USA
A. argyranthemi	T	KC584181	KC584378	KC584637	*Argyranthemum* sp.	New Zealand
A. armoraciae	T	KC584182	KC584379	KC584099	*Armoracia rusticana*	New Zealand
A. avenicola	T	KC584183	KC584380	KC584639	*Avena* sp.	Norway
A. axiaeritisporifera	T	KC584184	KC584381	KC584640	*Gypsophila paniculata*	Zealand
A. brassicae	R	KC584185	KC584382	KC584641	*Brassica oleracea*	USA
A. brassicicola	R	JX499031	KC584383	KC584642	*Brassica oleracea*	USA
A. calycipyricola	T	KC584186	KC584384	KC584643	*Pyrus communis*	China
A. carotiincultae	T	KC584188	KC584386	KC584645	*Daucus carota*	USA
A. cheiranthi	R	AF229457	KC584387	KC584646	*Cheiranthus cheiri*	Italy
A. chlamydospora	T	KC584189	KC584388	KC584647	Soil	Egypt
A. cinerariae	R	KC584190	KC584389	KC584648	*Ligularia* sp.	USA
A. conjuncta	T	FJ266475	KC584390	KC584649	*Pastinaca sativa*	Switzerland
A. cumini	T	KC584191	KC584391	KC584650	*Cuminum cyminum*	India
A. dauci	R	KC584192	KC584392	KC584651	*Daucus carota*	USA
A. daucifolii	T	KC584193	KC584393	KC584652	*Daucus carota*	USA
A. dianthicola	R	KC584194	KC584394	KC584653	*Dianthus allwoodii*	New Zealand
A. elegans	T	KC584195	KC584395	KC584654	*Lycopersicon esculentum*	Burkina Faso
A. ellipsoidea	T	KC584196	KC584396	KC584655	*Dianthus barbatus*	USA
A. eryngii	R	JQ693661	KC584397	KC584656	*Eryngium* sp.	-
A. ethzedia	T	AF392987	KC584398	KC584657	*Brassica napus*	Switzerland
A. gaisen	R	KC584197	KC584399	KC584658	*Pyrus pyrifolia* cv. Nijiseiki	Japan
A. geniostomatis	T	KC584198	KC584400	KC584659	*Geniostoma* sp.	New Zealand
A. helianthiinficiens	R	KC584200	KC584401	KC584660	*Helianthus annuus*	UK
A. gypsophilae	T	KC584199	KC584402	KC584661	*Gypsophila elegans*	–

Species name	Status[1]	Genbank (ITS)	Genbank (RPB2)	Genbank (TEF1)	Host / Substrate	Country
A. infectoria	T	DQ323697	KC584404	KC584662	*Triticum aestivum*	UK
A. japonica	R	KC584201	KC584405	KC584663	*Brassica chinensis*	USA
A. juxtiseptata	T	KC584202	KC584406	KC584664	*Gypsophila paniculata*	Australia
A. limaciformis	T	KC584203	KC584407	KC584665	Soil	UK
A. limoniasperae	T	FJ266476	KC584408	KC584666	*Citrus jambhiri*	USA
A. longipes	R	AY278835	KC584409	KC584667	*Nicotiana tabacum*	USA
A. macrospora	T	KC584204	KC584410	KC584668	*Gossypium barbadense*	USA
A. mimicula	T	FJ266477	KC584411	KC584669	*Lycopersicon esculentum*	USA
A. molesta	T	KC584205	KC584412	KC584670	*Phocaena phocaena*	Denmark
A. mouchaccae	T	KC584206	KC584413	KC584671	Soil	Egypt
A. nepalensis	T	KC584207	KC584414	KC584672	*Brassica* sp.	Nepal
A. nobilis	R	KC584208	KC584415	KC584673	*Dianthus caryophyllus*	New Zealand
A. oregonensis	T	FJ266478	KC584416	KC584674	*Triticum aestivum*	USA
A. panax	R	KC584209	KC584417	KC584675	*Aralia racemosa*	USA
A. perpunctulata	T	KC584210	KC584418	KC584676	*Alternanthera philoxeroides*	USA
A. petroselini	T	KC584211	KC584419	KC584677	*Petroselinum sativum*	–
A. photistic	T	KC584212	KC584420	KC584678	*Digitalis purpurea*	UK
A. porri	R	DQ323700	KC584421	KC584679	*Allium cepa*	USA
A. pseudorostrata	T	JN383483	KC584422	KC584680	*Euphorbia pulcherrima*	USA
A. radicina	T	KC584213	KC584423	KC584681	*Daucus carota*	USA
A. saponariae	R	KC584215	KC584425	KC584683	*Saponaria officinalis*	USA
A. selini	T	AF229455	KC584426	KC584684	*Petroselinum crispum*	Saudi Arabia
A. septorioides	T	KC584216	KC584427	KC584685	*Reseda odorata*	Netherlands
A. simsimi	T	JF780937	KC584428	KC584686	*Sesamum indicum*	Argentina
A. smyrnii	R	AF229456	KC584429	KC584687	*Smyrnium olusatrum*	UK

Species name	Status[1]	Genbank (ITS)	Genbank (RPB2)	Genbank (TEF1)	Host / Substrate	Country
A. solani	R	KC584217	KC584430	KC584688	*Solanum tuberosum*	USA
A. soliaridae	T	KC584218	KC584431	KC584689	Soil	USA
A. solidaccana	T	KC584219	KC584432	KC584690	Soil	Bangladesh
A. sonchi	R	KC584220	KC584433	KC584691	*Sonchus asper*	Canada
A. tagetica	R	KC584221	KC584434	KC584692	*Tagetes erecta*	UK
A. tenuissima	R	AF347032	KC584435	KC584693	*Dianthus* sp.	UK
A. thalictrigena	T	EU040211	KC584436	KC584694	*Thalictrum* sp.	Germany
A. vaccariae	R	KC584223	KC584438	KC584696	*Vaccaria hispanica*	USA
A. vaccariicola	T	KC584224	KC584439	KC584697	*Vaccaria hispanica*	USA
Stemphylium herbarum	O	KC584239	KC584471	KC584373	*Medicago sativa*	India