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REVIEW

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HARNESSING THE POTENTIAL OF NOVEL BIOACTIVE COMPOUNDS PRODUCED BY ENDOPHYTIC *Phoma* spp. – BIOMEDICAL AND AGRICULTURAL APPLICATIONS

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ABSTRACT

Endophytes are those inhabiting in plants without causing any apparent loss to the host plant. *Phoma* is a ubiquitously found genus of fungi in soil, water and air. Endophytic *Phoma* spp. are distributed with high specific diversity, those occur in plants and are mainly responsible for the production of a vast range of secondary metabolites. These secondary metabolites or the bioactive compounds have demonstrated a wide range of activity ranging from antibacterial, antifungal, antiviral, algicidal, cytotoxic, antitubercular and plant growth promoting, etc. Bioactive compounds are produced by *Phoma herbarum*, *P. sorghina*, *P. exigua*, *P. macrostoma*, *P. medicaginis*, *P. betae*, *P. tropica* and others. The present review emphasizes on different species of endophytic *Phoma* as novel source of bioactive compounds, and their applications in medicine and agriculture are documented.

Key words: endophytes, *Phoma*, secondary metabolites, bioactive compounds, antimicrobial and cytotoxic activities

INTRODUCTION

The term “endophyte” was introduced for the first time by De Bary [1866] and was applied to “any organisms occurring within plant tissues”. Nowadays, the most commonly used definition is that of Petrini [1991], “all organisms inhabiting plant organs that at some time in their life, can colonize internal plant tissues without causing apparent harm to the host”; however, there are many alternatives [Carroll 1988, Hirsh and Braun 1992, Wilson 1995, Moster et al. 2000, Schulz and Boyle 2005]. Broadly, these definitions include bacteria [Kobayashi and Palumbo 2000], fungi [Stone et al. 2000], algae [Trémouillaux-Guiller et al. 2002], insects [Tooker end Hanks 2004], and vascular plants [Marler et al. 1999]. However, majority of the endophyte research is focused on endophytic fungi, which represents the important and least explored group of microorganisms that have attracted increasing attention among researches due to their diverse metabolite profile in last few decades.

Endophytic fungi constitute a polyphyletic group of highly diverse fungi, which have been found in all plant families throughout the world, in all kinds of climates [Larran et al. 2016, Martinez-Klimova et al. 2017]. The hyperdiversity of endophytic fungi derives from that each individual plant species can be colonized with one or more fungal strains [Strobel and

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Daisy 2003, Strobel et al. 2008]. There are few reports on ascomycetous species, also describing some new mitosporic species [Jacob and Bhat 2000]. Mutualism, commensalism and parasitism are different modes of endophyte–host relationship. The symbiosis between plant and endophyte was ascertained, namely, the former protects and feeds the latter that produces 'in return' bioactive substances to enhance protection from pathogens, increase of nutrient uptake, and promotion of plant growth and stress tolerance of the host [Alvin et al. 2014]. The factors impacting plant–endophyte interactions include the mode of transmission, pattern of infection, plant age, environmental conditions, and genetic background. The vertically transmitted (systemic) endophytes from seeds are mutualistic, and horizontally transmitted (non-systemic) endophytes from spores are antagonistic to host. Moreover, during aging and senescence endophytic fungi becomes more pathogenic and widely cause external infections [Schardl et al. 1991, Saikkonen et al. 1998, Rai and Agarkar 2015]. Biological degradation of the dead and decaying host is the key role of endphytic fungi responsible for the nutrient recycling [Strobel 2002].

Endophytic fungi harbors a unique niche in a diverse environment making them an exceptional source of natural bioactive compounds [Strobel and Daisy 2003, Strobel et al. 2004]. The structure and function of host compounds are mimicked by endophyte metabolites [Strobel 2002], which can be provided directly to their hosts, thereby contributing to their chemical defense, or they might have transferred the corresponding genes to the host genome or *vice versa* [Wink 2008]. Most of the endophytes have the potential to synthesize various bioactive metabolites with therapeutic value, including those which have been already discovered: paclitaxel (also known as Taxol) [Stierle et al. 1993, Rebecca et al. 2011, Zaiyou et al. 2017], podophyllotoxin [Eyberger et al. 2006], deoxypodophyllotoxin [Kusari et al. 2009a], camptothecin and structural analogs [Puri et al. 2005, Kusari et al. 2009c, 2012, Shweta et al. 2010], hypericin and emodin [Kusari et al. 2008, 2009b], and azadirachtin [Kusari et al. 2012]. Moreover, they are also prolific producers of bioactive secondary metabolites demonstrating antimicrobial, antiparasitic and cytotoxic effects [Hensens et al. 1999, Garcia-Effron et al. 2009].

Exciting possibilities for exploiting endophytic fungi for the production of a plethora of known and novel biologically active secondary metabolites provide the impetus for a number of investigations and encourage scientists all over the world to figure out, how can endophytes be exploited for large scale *in vitro* production of high value phytochemicals under

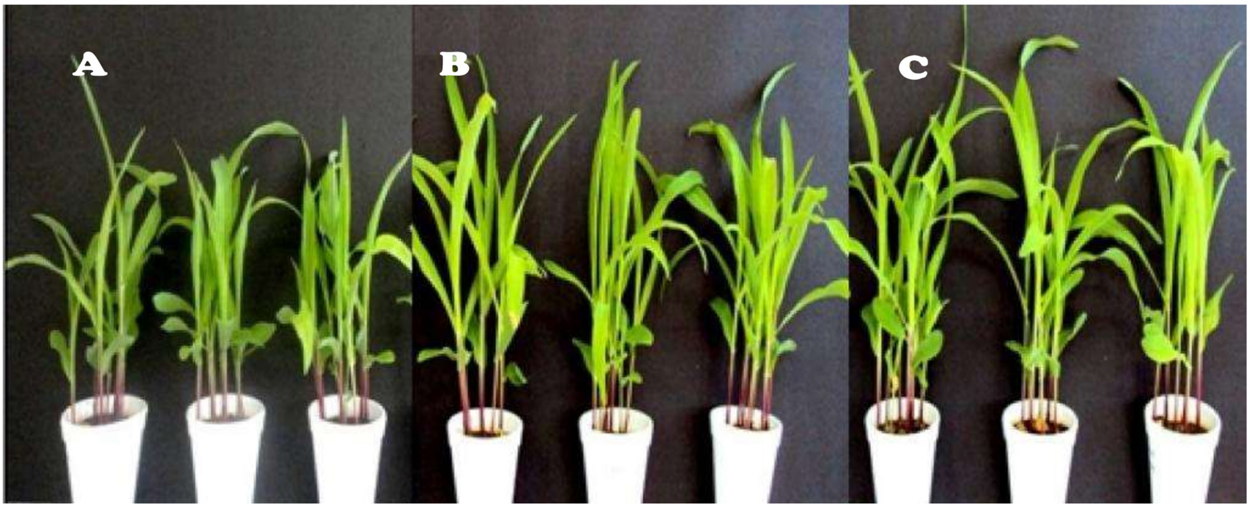

Fig. 1. Height difference of *Zea mays* plants: A. Control. B. Inoculated with extracts of *Phoma* species isolated from *T. cordifolia*. C. Inoculated with extracts of *Phoma* sp. isolated from *C. procera* [Open access source: Kedar et al. 2014]

various strategies that can be applied to sustain and enhance the product yield in these organisms?

The aim of the current review is indicating the importance of *Phoma sensu lato* endophytes as a promising source of biologically active metabolites, and their applications in medicine and agriculture.

Phoma AS ENDOPHYTES

The genus *Phoma* has always been considered as one of the major fungal genera having more than 3000 intrageneric taxa described [Monte et al. 1991]. After extensive studies carried out by Dutch mycologists number of species decreased, because they gave up the common practice of host associated nomenclature, and studied micro morphological characters on culture media [Boerema et al. 2004]. Significant progress has been made several years later to clarify generic boundaries among *Phoma* species and related genera. In 2009, the family *Didymellaceae* accommodated *Didymella*, *Ascochyta*, and *Phoma*, as well as several *Phoma*-like genera [Gruyter et. al. 2009, 2012, Aveskamp et al. 2010]. Molecular studies have revealed the heterogeneity of *Phoma*, and many species have been reclassified into *Coniothyriaceae* [Gruyter et. al. 2012], *Leptospahaeriaceae* [Gruyter et. al. 2012], *Cucurbitariaceae* [Gruyter et. al. 2010], *Phaeosphaeriaceae* [Gruyter et. al. 2010] and *Pleosporaceae* [Aveskamp et al. 2010, Gruyter et. al. 2012]. Therefore, only the species resided in the newly established family *Didymellaceae,* with the generic type of *Phoma herbarum* Westend., are considered as *Phoma sensu stricto* [Gruyter et. al. 2009, 2012].

Phoma sensu lato represents an extremely varied group of fungi and always occurring in economically important crops as an important fungal plant pathogenic complex. Several *Phoma* species are very significant, posturing serious problems to organizations that are concerned with plant health quarantine regulation [Koch and Utkhede 2004, Balmas et al. 2005]. Although the pathogenic nature of *Phoma* could be helpful, as a means of biocontrol agent of plant pathogens and weeds. The ubiquitous species *P. herbarum*, *P. exigua* and *P. macrostoma* may play a role as bioherbicide, effective against broadleaf weeds, such as chickweed (*Caryophyllaceae*), and dandelion (*Taraxacum* spp.) [Zhou et al. 2004, Stewart-Wade and Boland 2005, Hynes 2018], clematis (*Clematis vitalba*) [Paynter et al. 2006] and salal (*Gaultheria* spp.) [Zhao and Shamoun 2006]. Although most taxa are constantly present in the environment as saprophytic soil organisms, many of them switch to a pathogenic lifestyle when a suitable host is encountered [Aveskamp et al. 2008].

The genus also comprises species and strains which are recognized as endophytic, including terrestrial species associated with a wide range of hosts as well as almost completely unexplored habitat of *Phoma* spp. in the marine environment [Osterhage et al. 2000, Yarden et al. 2007, Rai et al. 2018]. *Phoma* endophytes are recognized as rich sources of secondary metabolites of multifold importance [Karsten et al. 2007, Strobel et al., 2011] including enzymes and plant growth hormones [Kedar et al. 2014]. Some of these metabolites are bioactive compounds that demonstrated potent anticancer, antibacterial, antifungal and cytotoxic activities. It is generally felt that plants growing in areas of higher biodiversity have the fate of housing *Phoma* endophytes with great biodiversity [Strobel et al. 2004]. Thus, tropical rainforest possessing the greatest biodiversity on the earth is an endophyte resources storehouse. Moreover, medicinal plants are reported as the important group of plants to harbor *Phoma* endophytes [Strobel 2002]. It is well known that the medicinal plants are the rich sources of precious bioactive compounds. As a consequence of long term association of endophytes with such plants, the former may also participate in metabolic pathways and enhance its own natural bioactivity or may gain some genetic information to produce specific biologically active compound similar to the host plant. Khan et al. [2007] investigated for endophytic mycoflora of *Calotropis procera*, a widely used medicinal plant in the Indian Sub-continent, as a great source of bioactive secondary metabolites. A total of eight fungal species viz., *Aspergillus niger*, *A. flavus*, *Aspergillus* sp., *Phoma chrysanthemicola*, *P. hedericola*, *Phoma* sp., *Penicillium sublateritium*, and *Candida albicans* were isolated. Among the endophytic mycobiota, *Phoma* was the most abundant genus. *Phoma* constituted the most frequently isolated endophytes from indigenous banana of wet tropics of North Queensland [Nisa et al. 2015], and had been reported in leaves of angio-

Table 1. Bioactive metabolites produced by endophytic *Phoma* species, their hosts and bioactivities

No.	Endophytic *Phoma* spp.	Host	Bioactive metabolites	Class of compound	Biological activity	Applications	References
1	2	3	4	5	6	7	8
1.	*Phoma tropica*	inner tissues of marine brown alga *Fucus spiralis*	–	5-hydroxyramulosin, 7-methoxycoumarin, $C_{10}H_{12}O_4$	antimicrobial activity against *A. niger*, *B. subtilis* and cytotoxicity against murine leukemia cells	development of antibiotics and anticancer drug formulations	Osterhage et al. (2002), Santiago et al. (2012)
2.	*Phoma* sp. NRRL 25697	isolated from the stromata of *Hypoxylon* spp.	–	phomadecalins A, B, C and D, phomapentenone A	antibacterial activity against Gram-positive bacteria, viz., *B. subtilis* and *S. aureus*	antibiotic substitute against Gram-positive bacteria	Che et al. (2002)
3.	*Phoma* sp. JS752	*Phragmites communis* Trinius collected from a swamp at Seochun, South Korea	polyketide	barceloneic acid C	antibacterial activity against pathogenic Gram-positive bacteria including *Bacillus cereus* (13061), *Listeria monocytogenes* (19114) and *Staphylococcus pseudintermedius* (49444), as well as Gram-negative bacteria including *Escherichia coli* (35150) and *Salmonella typhimurium* (43174)	potent antibiotic against human pathogenic bacteria (both Gram-positive and Gram-negative)	Xia et al. (2014)
4.	*Phoma* sp.	*Taxus wallichiana* (Himalayan Yew), Singhe-To, Khatmandu, Nepal	–	altersolanol A, 2-hydroxy- -6-methyl benzoic acid	antibacterial activity against *B. subtillis*	active against *Pseudomonas aeruginosa* and *Bacillus* spp.	Yang et al. (1994)
5.	*Phoma* sp. L28	mangrove plant roots of *Myoporum bontioides* A	anthraquinone derivative	7-(γ,γ)-dimethylallyl oxymacrosporin ($C_{21}H_{20}O_5$) and derivatives	antifungal activity against *Colletotrichum musae* (Berk. & M.A. Curtis) Arx., *Colletotrichum gloeosporioides* (Penz.) Sacc., *Fusarium graminearum* Schw., *Penicillium italicum* Wehme, *Fusarium oxysporum* Schlecht. f. sp. *lycopersici* (Sacc.) W.C. Snyder et H.N. Hansen, and *Rhizoctonia solani* Kuhn	potential substitute for carbendazim	Huang et al. (2017)
6.	*Phoma medicaginis*	surface-sterilized shoots of *Medicago sativa* and *M. lupulina*	–	brefeldin A	active against *Absidia glauca* and *Fusarium culmorum*, and various phylloplane fungi	development of antifungal against phytopathogenic fungi	Weber et al. (2004)

7.	*Phoma* sp. ZJWCF006	*Arisaema erubescens*	α-tetralone derivative	(3S)-3,6,7-trihydroxy--a-tetralone	antifungal activity against *Fusarium oxysporium*, *Rhizoctonia solani*, *Colletotrichum gloeosporioides*, and *Magnaporthe oryzae*, non-cytotoxic	fungicide for plant pathogenic fungi	Wang et al. (2012)
8.	*Phoma* sp.	*Arisaema erubescens*	amide derivative	cercosporamide	antifungal and moderately cytotoxic to HT-29, SMMC-772, MCF-7, HL-60, MGC80-3, and P388	fungicide for plant pathogenic fungi, anticancer drug formulations	Wang et al. (2012), Hoffman et al. (2008), Kiprono et al. (2000), Michael et al. (1992), Tijerino et al. (2011), Melmed et al. (1985)
9.	*Phoma* sp.	*Arisaema erubescens*	sterol	β-sitosterol	broad-spectrum antifungal activity		
10.	*Phoma* sp.	*Arisaema erubescens*	–	trichodermin	broad-spectrum antifungal activity		
11.	*Phoma* sp.	*Larrea tridentata* (creosote bush)	volatile organic compounds (VOCs)	sesquiterpenoids, some alcohols and several reduced naphthalene derivatives	*Aspergillus flavus*, *Botrytis cinerea*, *Ceratocystis ulmi*, *Pythium ultimum*, *Phytophthora palmivora*, *Sclerotinia sclerotiorum*, etc.	fungicide against crop pathogens	Strobel et al. (2011)
12.	*Phoma* sp.	*Fagonia cretica*	pyrenophorol	macrolide pyrenophorol (synonym helmidiol) (4S,7R)-4,7-dihydroxyoctanoic acid and 2,3,10,11-tetrahydro-pyrenophorol	active against the Gram-positive bacterium *Bacillus megaterium*, the fungus *Microbotryum violaceum*, and the alga *Chlorella fusca*	antibiotic and algicide formulation	Krohn et al. (2007)
13.	*Phoma* sp.	–	macrodiolides	pyrenophorol (1), (–)-dihydro-pyrenophorin (3),	activity against the fungus *Microbotryum violaceum*, the alga *Chlorella fusca*, and the bacteria *Escherichia coli* and *Bacillus megaterium*	fungicidal, antibacterial and algicidal formulation	Zhang et al. (2008), Qin et al. (2010)
			analogues	4-acetylpyrenophorol (2), 4-acetyldihydropyrenophorin (4), cis-dihydropyrenophorin (5), and tetrahydropyrenophorin (6)			
			ring-opened derivatives	seco-dihydropyrenophorin (7), 7-acetylseco-dihydropyrenophorin (8), and secodihydropyrenophorin-1,4-lactone (9)			

1	2	3	4	5	6	7	8
14.	*Phoma* Sacc. emend. Boerema & G.J. Bollen	*Glycyrrhiza glabra* Linn.	two thiodiketopiperazine derivatives	–	antibacterial activity against *Staphylococcus aureus* and *Streptococcus pyogenes*	as a substitute for antibiotics like ciprofloxacin and ampicillin	Arora et al. (2016)
15.	*Phoma* sp.	*Cinnamomum mollissimum*	polyketide	5-hydroxyramulosin	inhibiting fungal pathogen *Aspergillus niger*	–	Santiago et al. (2012)
16.	*Phoma betae*	*Ginkgo biloba*	diterpene	Taxol	cytotoxic against breast cancer cells (MCF-7, ATCC HTB-22), lung adenocarcinoma cells (A549, ATCC CCL-185), and glioblastoma cells (T98G, ATTCC CRL–1690)	anticancer drug development	Kumaran et al. (2012)
17.	*Phoma medicaginis*	*T. wallichiana* var. *mairei*	Taxol-diterpene	paclitaxel	cytotoxic to murine adenocarcinoma model, 9KB (human oral epidermoid carcinoma, *in vivo* activity against P1534 leukemia	used against breast and non-small cell lung cancers and in Kaposi's sarcoma	Zaiyou et al. (2017), Lasala et al. (2006), Oberlie and Kroll (2004)
18.	*Phoma* sp. PT01	leaves of *Mitragyna javanica* Koord and Val.	crude extract	Taxol	potentially cytotoxic against Jurkat, Kato III cells	*in vitro* anticancer study	Pharamat et al. (2013)
19.	*Phoma sorghina*	*Tithonia diversifolia* (Asteraceae)	anthraquinones and dendryols	1,7-dihydroxy-3-methyl-9,10--anthraquinone, 1,6-dihydroxy--3-methyl-9,10-anthraquinone, 1-hydroxy-3-methyl-9,10-anthraquinone, 1,7-dihydroxy-3-hydroxymethyl--9,10-anthraquinone; and dendryols E and F	phytotoxic against barnyardgras, significant cytotoxic activity against colon cancer and leukemia cell lines	–	Bick and Rhee (1966), Borges and Pupo (2006), Ge et al. (2005)
20.	*Phoma* sp. NRRL 46751	*Saurauia scaberrinae*	alkaloids	phomapyrrolidones A–C	antitubercular	–	Wijeratne et al. (2013)

21.	*Phoma* sp. YE3135	roots of *Aconitum vilmorinianum*	14-nordrimane-type sesquiterpenoid	phomanolide ((–)-6-methoxymellein, 7-hydroxy-3, 5-dimethyl-isochromen-1-one, norlichexanthone, 6-methylsalicylic Acid, gentisyl alcohol)	antiviral activities against influenza A virus	*in vitro* antiviral study against influenza H1N1 virus	Liu et al. (2019)
22.	*Phoma herbarum*	salt-stressed soybean plants	gibberellins	gibberellic acid (GA) 1, 3, 4, 7, 9, 12, 15, 19, 20	growth promotion in rice plants, and maize	formulation of growth promoter for soy bean crop under salt stress	Muhammad et al. (2009), Kedar et al. (2014)
23.	*Phoma* sp.	*Caralluma acutangula*, *Rhazya stricta*, and *Moringa peregrina*	–	indole-3-acetic acid (IAA)	plant growth promoter	–	Khan et al. (2017)
24.	*Phoma glomerata*	wheat plant	–	–	antifungal against *Fusarium graminearum* and *Fusarium culmorum*	biological control agent against Fusarium head blight (FHB) causing fungi	Comby et al. (2017)
25.	*Phoma eupatorii* isolate 8082	different plant species	extracellular metabolite cocktail	–	antifungal activity against broad range of *Phytophthora* spp.	broad spectrum biocontrol agent and anthocyanin inducer	Vries et al. (2018)

sperm and gymnosperm trees in four types of tropical forests in the Western Ghats [Suryanarayanan et al. 2002]. Endophytic *Phoma* strains have been isolated by Bharathidasan and Panneerselvam [2011] from *Avicennia marina* a dominant mangrove species in Karankadu. Vieira et al. [2012] reported diversity and antimicrobial activity of endophytic fungi isolated from traditional Brazilian medicinal plant *Solanum cernuum. Phoma glomerata* and *P. moricola* have been reported as one of the most abundant species. De Siqueira et al. [2011] studied the leaves and stems endophytic fungi from *Lippia sidoides*, an antiseptic medicinal plant used in the northeast of Brazil. Among fungi recovered from stems, *Phoma tracheiphila* was dominant, followed by *Fusarium lateritium*.

Phoma endophytes plays a potential role in promoting plant growth through different mechanisms [Rai et al. 2013, 2014], mainly through the production of ammonia and phytohormones including indole-3-acetic acid (IAA). Generally, IAA acts as plant growth promoter which enhances both cell elongation and cell division, and is essential for plant tissues differentiation. Moreover, it can also augment photosynthesis by modulation of endogenous sugar and abscisic acid (ABA) signal. Particularly, medicinal plants produce growth enhancer bioactive compounds like GA3 (gibberellin), IAA (indole-3-acetic acid), ABA (abscisic acid), Z (zeatin), ZR (zeatin riboside). The endophytes isolated from that group of plants can be applied for growth promotion activity. The endophytic *Phoma glomerata* LWL2 significantly promoted the shoot and allied growth attributes of GAs-deficient dwarf mutant *Waito-C* and Dongjin-beyo rice. Analysis of the pure culture of this fungus showed biologically active GAs (GA_1, GA_3, GA_4 and GA_7) in various quantities [Waqas et al. 2012a]. Two endophytic *Phoma* species from *Calotropis procera* and *Tinospora cordifolia* enhanced growth of maize plants, also demonstrated encouraging effect on germination of maize seeds [Kedar et al. 2014].

Phoma endophytes produce a plethora of volatile organic compounds (VOCs). For example, *Phoma* sp. isolated and characterized as endophyte of *Larrea tridentata* (creosote bush) growing in the desert region of Southern Utah, USA, produces a unique mixture of (VOCs), including some alcohols, a series of sesquiterpenoids, and several reduced naphthalene derivatives. These substances demonstrated biological activity, and also potential as a biofuel – Mycodeisel^{TM} [Strobel et al. 2011, Gupta et al. 2016].

So far, several bioactive compounds from endophytic *Phoma* spp., which demonstrated antimicrobial activity, have been reported. Phomodione, cercosporamide and usnic acid were isolated from culture broth of a *Phoma* species, discovered as an endophyte of Guinea plant (*Saurauia scaberrinae*). These compounds exhibited antibiotic activity against *Staphylococcus aureus* and were active against a representative oomycete, ascomycete and basidiomycete *Pythium ultimum*, *Sclerotinia sclerotiorum*, and *Rhizoctonia solani* [Hoffman et al. 2008]. The endophytic *Phoma* species ZJWCF006 has been isolated from *Arisaema erubescens* in China [Wang et al. 2012]. This strain produced different varieties of metabolite that demonstrated strong and moderate antifungal and cytotoxic activities. (3S)-3,6,7-trihydroxy-α-tetralone, showed antifungal activities, while cercosporaminde, β-sitosterol trichodermin has broad spectrum of antifungal and antitumor activities [Wang et al. 2012]. Karsten and colleagues [2007] reported antifungal and algaecidal activity of pyrenophorol (synonym helmidiol), 2,3,10,11-tetrahydropyrenophorol, and (4S,7R)-4,7-dihydroxyoctanoic acid, isolated from an endophytic *Phoma* sp. recovered from *Fagonia cretica* Gomera (Spain). Gubiani et al. [2017] reported (10′*S*)-verruculide B, vermistatin, dihydrovermistatin production by the endophytic *Phoma* sp. nov. LG0217 obtained from *Parkinsonia microphylla* in presence of epigenetic modifier histone deacetylase (HDAC) inhibitor, suberoylanilide hydroxamic acid (SAHA). In absence of epigenetic modifier it produces (*S*,*Z*)-5-(3′,4′-dihydroxybutyldiene)-3-propylfuran-2(5*H*)-one and nafuredin. Zakaria and Aziz [2018] reported the endophytic *Phoma* sp. from banana leaves (*Musa* sp.) and identified them by ITS sequencing.

APPLICATIONS OF BIOACTIVE COMPOUNDS PRODUCED BY ENDOPHYTIC *Phoma* spp. IN BIOMEDICAL AND AGRICULTURE

The phytochemicals derived from the endophytic *Phoma* spp. can be explored immensely for their bioactivities. These secondary metabolites or the bioactive compounds have demonstrated an extensive range of *in vitro* activity ranging from antibacterial, antifungal, antiviral, algaecidal, cytotoxic, antitubercular and plant growth promoting, etc. Bioactive compounds are synthesized from *Phoma herbarum*, *P. sorghina*, *P. exigua*, *P. macrostoma*, *P. medicaginis*, *P. betae*, *P. tropica* etc. Many researchers have already reported an *in vitro* antibacterial and antifungal activity of compounds like 5-hydroxyramulosin [Osterhage et al. 2002, Santiago et al. 2012], 7-methoxycoumarin, phomadecalins A, B, C and D, phomapentenone A, barceloneic acid C, altersolanol A, 2-hydroxy-6-methyl benzoic acid, 7-(γ,γ)-dimethylallyl oxymacrosporin and derivatives [Che et al. 2002, Xia et al. 2014, Huang et al. 2017], brefeldin A [Weber et al. 2004], cercosporamide, β-sitosterol sesquiterpenoids, some alcohols and several reduced naphthalene derivatives. *Glycyrrhiza glabra* Linn. is a traditional medicinal plant known for its ethanopharmacological value [Hosseinzadeh and Nassiri-Asl 2015]. The endophytic *Phoma* sp. obtained from *G. glabra* was identified on the basis of cultural, morphological and ITS sequencing as a species *Phoma* Sacc. emend. Boerema & G.J. Bollen, most closely related to *Phoma cucurbitacearum*. The fungal extract was designated as GG1F1 which showed significant antimicrobial activity. The active antimicrobial compounds were isolated and characterized as two thiodiketopiperazine derivatives. These compounds inhibited biofilm formation and the growth of pathogens like *Staphylococcus aureus* and *Streptococcus pyogenes*, with IC_{50} values of less than 10 µM. Both the compounds showed *in vitro* inhibition of bacterial transcription/translation and inhibited staphyloxanthin production in *S. aureus*. Thus, this antibacterial activity of the isolated thiodiketopiperazine derivatives can be explored as an antibiotic [Arora et al. 2016]. The compounds like macrolide pyrenophorol (4S,7R)-4,7-dihydroxyoctanoic acid and 2,3,10,11-tetrahydropyrenophorol have shown to be a potent antifungal [Santiago et al. 2012] and algicidal [Krohn et al. 2007, Zhang et al. 2008, Qin et al. 2010, Zhang et al. 2012]. These metabolic compounds can be used in medicine for the *in vitro* and *in vivo* applications. *Aconitum vilmorinianum* is a perennial herb and used in treatment of rheumatism and pains. The extract of the fungal strain *Phoma* sp. YE3135, derived from *A. vilmorinianum* contained new rare 14-nordrimane-type sesquiterpenoid, named phomanolide, (–)-6-methoxymellein, 7-hydroxy-3,5-dimethyl-isochromen-1-one, norlichexanthone, 6-methylsalicylic acid and gentisyl alcohol. Out of these phomanolide and (–)-6-methoxymellein possess *in vitro* antiviral activity against H1N1 influenza virus with IC_{50} values of 2.96+/–0.64 and 20.98+/–2.66 µg/mL, respectively [Liu et al. 2019].

Hamzah and colleagues [2018] reported the highest antifungal activity of *Phoma* sp. among the isolated endophytic fungi from the malayasian mangrove plant *Rhizophora mucronata*, against *Fusarium solani* (percent inhibition of 69.64%). The diterpenes like Taxol and paclitaxel obtained from different endophytic *Phoma* spp., also have shown their distinguishing cytotoxic activity against several cancerous cell lines including breast cancer cells (MCF-7, ATCC HTB-22), lung adenocarcinoma cells (A549, ATCC CCL-185), and glioblas-toma cells (T98G, ATTCC CRL–1690) and cytotoxic to murine adenocarcinoma model, 9KB (human oral epidermoid carcinoma, *in vivo* activity against P1534 leukemia [Oberlie and Kroll 2004, Lasala et al. 2006, Kumaran et al. 2014, Zaiyou et al. 2017]. The anthraquinones and dendryol derivatives like 1,7-dihydroxy-3-methyl-9,10-anthraquinone; 1,7-dihydroxy-3-hydroxymethyl-9,10-anthraquinone; 1-hydroxy-3-methyl-9,10-anthraquinone; 1,6-dihydroxy-3-methyl-9,10-anthraquinone; and dendryols E and F are found to be significantly cytotoxic against colon cancer and leukemia cell lines [Bick and Rhee 1966, Ge et al. 2005, Borges and Pupo 2006].Thus, demonstrating their fruitful application in treatment of cancer in humans.

The bioactive compounds produced by different *Phoma* spp. also play a significant role in agriculture. For example, the Gibberelins family compounds have been obtained from *Phoma herbarum,* Gibberellic acid 1,3,4, and other derivatives have shown their plant growth promoting activity in rice and maize [Hamayun et al. 2009, Kedar et al. 2014]. Waqas and coworkers [2012b] reported gibberelins and indole-3-acetic acid from endophytic *Phoma*, for plant growth promoting activity during stress conditions, thus demonstrating their potential use in agriculuture.

Studies carried out by Vries and coworkers [2018], regarding endophytic fungi isolated from different plant species and screened for their metabolite secretion showed their biological activity. Among the isolated endophytes *Phoma eupatorii* isolate 8082 was the most promising against *Phytophthora infestans* a major pathogen of cultivated tomato (*Solanum lycopersicum*) and cultivated potato (*Solanum tuberosum*). *Phytophthora eupatorii* shows almost complete inhibition of *P. infestans in vitro* and *in planta*. *P. eupatorii* produces extracellular anti-*Phytophthora* compounds as well as enhances the plant defense mechanism by promoting anthocyanin production. A vast range of *Phytophthora* spp. is inhibited by *P. eupatorii* indicating their role as a broad spectrum biocontrol agent against *Phytophthora* spp. Authors reported the highest inhibition of *Phytophthora* by *P. eupatorii* (50.6 ±2.2%) and *Monosporascus* sp. was the lowest (11.9 ±1.6%).

The endophytic *Phoma glomerata* and other fungi obtained from wheat plants were screened for their antifungal activity against Fusarium head blight (FHB) causing *Fusarium graminearum* (30–51% inhibition) and *Fusarium culmorum* (15–53% inhibition). This study on detached wheat spikelets revealsendophytic *Phoma* spp. as a biological control agent against FHB pathogens [Comby et al. 2017]. Khan et al. [2017] reported indole-3-acetic acid produced by *Phoma* endophytes isolated from medicinal plants including *Caralluma acutangula, Rhazya stricta*, and *Moringa peregrina*, that showed improved seed germination and mitigating oxidative stress in host. These important plant growth promoters from endophytic *Phoma* represent an outstanding example of significant use of endophytic *Phoma* in agriculture [Khan et al. 2017].

CONCLUSIONS

To sum up, several bioactive compounds from endophytic *Phoma* spp., which demonstrated biological activity, have been discussed. It is evident that the endophytic *Phoma* can be explored for the production of bioactive phytochemicals to harness their *in vitro* bioactivities, which is a green approach and can be a better substitute for the present synthetic chemicals used in medicine and agriculture. Although, the functions and activities of many of the metabolites have been demonstrated *in vitro* as well as *in vivo,* there are still many bioactive metabolites from endophytic *Phoma* spp. whose functions are unknown, and therefore, there is a greater need to screen these bioactive compounds to find out antiinflammatory, antioxidant, antiviral, anticancer, cardiovascular, and immunomodulatory activities. In agriculture their potential can be further explored as plant growth promoters, and biocontrol agents for insect pests and diseases. Further research on synthesis of secondary metabolites and analysis of their biological activity would improve our understanding of how the endophytic *Phoma* could be a valuable source of biologically active compounds.

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