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Endophytic *Diaporthe* (*Phomopsis*): a treasure genus of bioactive compounds

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Fungal endophytes are a group of fungi that grow inside the tissues of plants without showing any symptoms of illness. They are potent sources of plentiful and varied bioactive secondary metabolites. Irrespective of host tissue, collection localities, and seasons, the genus *Diaporthe* (syn. *Phomopsis*) has been isolated as an endophytic fungus from a diverse host range. A wide range of primarily bioactive secondary metabolites are known to be produced by this genus through several complex metabolic activities. These compounds are often well appreciated for their antitumor, cytotoxic, antimalarial, and antibiotic activities, leading to drug discovery. Moreover, it has been reported for various applications in bioremediation, enzyme production, and plant protection. In this review, we summarise isolation and beneficial bioactivities reported for the *Diaporthe* and *Phomopsis* like forms.

Keywords : Antibiotic, bioactivities, cytotoxic, *daiporthe,* host, metabolites, plant protection.

INTRODUCTION

Endophytes reside within the living host tissues and show interactions ranging from mutualistic to latent pathogenic relationships with the host. Over the last few decades, our understanding of plant-microbe interaction has increased several fold, primarily due to the potential benefits that humans might derive from these endophytic associations (Selim *et al.* 2012). Endophyte's capabilities to synthesize a vivid class of bioactive compounds with a wide range of medical applications have proven their worth as a strategically promising bioresource with substantial economic potential for the pharmaceutical and agrochemical sectors (Gouda *et al.* 2016).

The latest advancements in screening methods suggest that endophytes possess a vast reservoir of varied metabolites (Aly *et al.* 2011; Zhang *et al.* 2012). Furthermore, natural compounds of endophytic origin possessing distinct chemical structures suggest the formation of these microbe's chimeric metabolic machinery (Gunatilaka, 2006). There are 2–11 million estimated fungal species on the planet, yet only formally described taxa are around 150,000, a minute fraction of the total estimate (Aly *et al.* 2011, Phukhamsakda *et al.* 2022).

According to a report, more than 300 naturally occurring compounds were isolated from endophytes between 1987 and 2006 (Zhang *et al.* 2006). *Diaporthe* species and their asexual forms, *Phomopsis*, are ubiquitous and infect a broad host range. They can act as saprobes, endophytes, or pathogens in plants and are also capable of infecting humans and other mammals. Historically, mycologists and plant pathologists used the generic names *Diaporthe* (sexual morph) and *Phomopsis* (asexual morph) but as an implementation of "One fungus, one name" principle (Rossman *et al.* 2015), *Diaporthe*, being the older name, takes precedence over *Phomopsis*. According to

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Chepkirui and Stadler (2017) the term "Phomopsis-like" should be referred to describe conidial state. In this review, to avoid confusion, wherever required, *Phomopsis* sp. is used when the literature specifically reports them under that name. Many species of *Diaporthe* that appear morphologically similar have been shown to be genetically distinct (van Rensburg *et al.* 2006). In addition, isolates previously identified solely on the basis of host association were later demonstrated to represent different taxa (Hyde *et al*. 2014). This highlights that *Diaporthe* is a highly complex genus comprising numerous cryptic species that cannot be reliably separated using morphology or host specificity alone. Recent taxonomic studies increasingly rely on molecular phylogenetic analyses to delimit species boundaries within *Diaporthe*. A multigene approach has proven particularly effective, with five loci commonly employed: the internal transcribed spacer region (ITS), translation elongation factor 1-α (TEF1-α), tubulin (TUB2), calmodulin (CAL), and histone H3 (HIS) (van Rensburg *et al.* 2006; Santos *et al.* 2010, Udayanga *et al.* 2011, Gomes et al. 2013). The integration of these gene regions provides improved phylogenetic resolution and supports the recognition of cryptic species under the phylogenetic species concept. More than 1200 taxa under *Diaporthe* and almost 1000 species under *Phomopsis* are now listed by Index Fungorum (www.indexfungorum.org) and MycoBank (www.mycobank.org) (accessed in April 2024) (Dissanayake *et al.* 2024).In tropical regions, *Diaporthe* or its asexual form *Phomopsis* has been isolated as an endophyte from a wide range of host plants, including pteridophytes, mangroves, and seaweeds (Huang *et al.* 2008a; Erbert *et al.* 2012; Kumaresan *et al.* 2013; Luo *et al.* 2016; Cai *et al.* 2017; Gao *et al.* 2019; Guo *et al.* 2023; Khan *et al.* 2023) irrespective of location, tissues, and collection seasons (Bussaban *et al.* 2001; Suryanarayanan *et al.* 2002; Tomita 2003; Murali *et al.* 2006; Rossman *et al.* 2007; Botella and Diez 2011; González and Tello 2011; Nimbalkar and Singh 2022). As a natural bio manufacturer and source of significant medicinal compounds, *Diaporthe* sp. has gained the interest of researchers in recent times (Hilario and Goncalves, 2022; Murali 2006; Botella and Diez, 2011; Singh *et al.* 2017; Kharwar, 2022; Nimbalkar and Singh, 2023; Nimbalkar and Mukherjee 2025). It is easily adapted to an endophytic mode of livingin both temperate and tropical climates. However, they are prevalent in the sapwood of angiosperms.

This review aims to focus on the systematic study of the endophytic fungus *Diaporthe* including its diversity, host ranges, bioactive chemicals and role in drug discovery, plant protection, bioremediation and pharmacological applications such as anti-microbial, antimalarial, and cytotoxic compounds.

METHODOLOGY

The literature published between 1975 and 2024 was systematically collected from PubMed and Google Scholar. The search included articles from major academic publishers such as Springer Nature, Taylor & Francis, ScienceDirect, Elsevier, Wiley, and other recognized scientific sources.The key words used to search the literature such as *Phomopsis* and *Diaporthe* and its antimicrobial, antitumour, anti-inflammatory, antioxidant, immunomodulatory activities and the chemical compounds.

Taxonomy of *Phomopsis*

Kingdom:	Fungi
Phylum:	Ascomycota
Class:	Sordariomycetes
Order:	Diaporthales
Family:	Diaporthaceae
Genus:	*Diaporthe* (syn. *Phomopsis)*

HABITAT/ECOLOGY

Within the fungal kingdom, the genus *Diaporthe* sp. has several species, most of which are found in tropical and subtropical climates (Gomes *et al.* 2013; Udayanga *et al.* 2011; Chepkirui*et al.* 2017; Dissanayake *et al.* 2024). *Diaporthe* sp.encompasses more than 1000 species worldwide inhabiting a more comprehensive range of host tissues (Uecker 1988; Rehner and Uecker, 1994; Mostert *et al.* 2000; Crous 2005; Rossman *et al.* 2007; Rossman and Palm-Hernández, 2008). This genus is also known for

its pathogenicity in both humans and plants, and often remains as endophyte or saprobe (Van Warmelo *et al.* 1970; Uecker, 1988; Rehner and Uecker ,1994; Sutton *et al.* 1999; Garcia-Reyne *et al.* 2011). Due to the ability to switch their lifestyle, *Diaporthe* species can be found on the same or different hosts as endophytes in asymptomatic tissues or as phytopathogens (Sessa *et al.* 2018; Udayanga *et al.* 2011). For example, *D. phaseolorum* is pathogenic to soybean (Santos *et al.* 2011), but endophytic in mangroves (*Laguncularia racemosa)* (Sebastiane *et al.* 2011). They have been isolated from dead material as saprobes and live tissues of the same or different hosts as endophytes (Promputtha *et al.* 2007; Udayanga *et al.* 2011).

Ubiquitous nature of Diaporthe as an endophyte

Various species of *Diaporthe* have been reported as endophytes from different hosts and parts of the plants. *Diaporthe* sp. has been documented as a dominant genus along with *Colletotrichum gloeosporioides, Glomerella* sp., Xylariaceous fungi in *Amomum siamense* (Bussaban *et al.* 2001) and in plants like *Tectona grandis* and *Samanea saman* Merr (Chareprasert *et al.* 2006) of various age groups, or even from *Acer ginnala* (Qi *et al.* 2012). As endophytes, *Diaporthe* species have been isolated from agricultural, medicinal and ornamental plants growing in a wide variety of locations and habitats (Huang *et al*. 2015; Dos Santos *et al*. 2021; Yang *et al*. 2018). Chareprasert *et al.* (2006) found that *Phomopsis* sp. was the most frequent endophytic fungus isolated from young and adult leaves of *Tectona grandis* and *Samanea saman* Merr. This suggests that the endophytes have evolved adaptations to withstand various host defenses. Ilyas *et al.* (2019) documented this genus from trees of tropical areas and others, unequivocally confirming the association of this genus with different plant groups such as angiosperms, gymnosperms, pteridophytes, mangroves, seed weed etc (Huang *et al.* 2008; Erbert *et al.* 2012; Cai *et al.* 2017; Gao *et al.* 2019; Guo *et al.* 2023). The dominant nature of endophytic *Diaporthe* sp.in various hosts has been confirmed from time to time in different studies (Azevedo *et al.* 2000; Verma *et al.* 2007; Huang *et al.* 2008a; Wenzel *et al.* 2010; Verma *et al.* 2014; Singh *et al.* 2017; Ilyas *et al.* 2019; Gao *et al.* 2019). Singh *et al.* (2017) studied endophytic assemblages of *Tectona grandis* tissues. According to their findings, *Phomopsis* spp. have constituted most of the endophytic assemblage in teak tissues. The most common species was *Phomopsis* sp. 3 *Phomopsis longicolla* (syn. *Diaporthe longicolla*), which accounted for 21.1% of the assemblage, followed by (*Phomopsis* sp. 1) (12.38%). Members of this species complex colonized about 60% of the investigated tissue sections. It was inferred from these observations that the rapid growth of *Phomopsis* and the slower rate of growth of other species might have yielded such better occupancy in the host tissue.Further more, *Phomopsis* spp. have been consistently documented as dominant endophytes of teak (*Tectona grandis*), supporting the hypothesis of a potential co-evolutionary relationship with the host species (Saikkonen *et al.* 2004).

Several investigations confirmed the endophytic nature of *Phomopsis* (Muller and Hallaksela , 1998; Wipornpan *et al.* 2001; Aveskamp *et al.* 2008). Ilyas *et al.* (2019) studied endophytic assemblages from roots, stems, barks, leaves, and fruits of 12 medicinal plants from North Sumatra. Among the 88 isolated strains of endophytic fungi, 52 (59%) studied by them were coelomycetes and were classified morphologically into five genera: *Colletotrichum*, *Phoma*, *Neopestalotiopsis*, *Phomopsis*, and *Phyllosticta*. Additionally, it was shown that most of the fungal endophytic strains collected belonged to the genus *Phomopsis*, of which 30% (27/88) were recovered from eight different species of medicinal host plants. Kokaew *et al.* (2011) recorded *Phomopsis arnoldiae* as an endophyte isolated from leaves of the forest tree *Ascistrocladus tectorius* in Khao Yai National Park,Thailand.

They found 72 isolates of endophytic *Phomopsis* spp. from forest trees and healthy wildplants from different habitats. Overall, 24 of the 31 morphospecies of sterile endophytes from *Magnolia liliflora* (Magnoliaceae) that were discovered by molecular phylogeny were assigned to the genus *Phomopsis* (Promputtha *et al.*

Table 1 : *Diaporthe* (*Phomopsis)* endophytes and their compounds with bioactivities

Diaporthe (Phomopsis) sp.	Host	Activities	Compounds	Reference
Phomopsis oblonga	*Gyrostroma missouriense*	Antibacterial	Nectriapyone	Nair & Carey 1975
Phomospsis sp.	*Cavendishia pubescenes*	-	Paspalitrems A and C	Bills *et al.* 1992
Phomopsis sp.	*Salix gracilostyla* var. *melanostachys*	Antibacterial	phomopsichalasin	Horn *et al.* 1995
Phompsis sp.	*Teucrium scorodonia*	Antibacterial	Phomosines A-C	Krohn et al. 1995
Phomopsis sp.	*Salix* sp.	-	Phomopsolide B & phomodiol	Horn *et al.* 1996
P.longicolla	*Dicerandra frutescens*	Antibacterial	Dicerandrols A–C	Wagenaar & Clardy 2001
Phomopsis sp.	Teak	Antimalarial Antitubercular Cytotoxicity	phomoxanthone A and phomoxanthone B	Isaka *et al.* 2001
Phomopsis sp.	*Erythrina crista-galli*	Antifungal, Antibacterial Cytotoxic	Phomol	Weber *et al.* 2004
Phomopsis sp.	*Aspidosperma tomentosum* *Spondias mombin*	Antibacterial	-	Corrado & Rodrigues 2004
P. cassia	-	Antifungal, Anti-cancer	Phomopsilacton, triterpenoids	Silva *et al.* 2005
Phomopsis sp.	*Erythrina crista-galli*	-	benzopyran-8-methanol derivative (68)	Weber *et al.* 2005
P. cassia	- -	Antifungal	Ethyl 2,4-dihydroxy-5,6-dimethylbenzoate, phomopsilactone	Silva *et al.* 2005
P. cassiae	*Cassia spectabilis*	Antifungal	Cadinane sesquiterpenes derivatives	Silva *et al.* 2006
Diaporthe sp.	Tea plant	Antibacterial	Cytoskyrins A (1)	Agusta *et al.* 2006.
*Diaporthe*sp.	-	-	Phomopsichalasin or diaporthichalasin (42)	Pornpakakul *et al.* 2007
Phomopsis sp.	*Garcinia dulcis*	Anti-microbial	Phomoenamide, Phomonitroester and Deacetylphomoxanthone B, dicerandrol A, (1S,2S,4S)-p-menthane-1,2,4-triol and uridine	Rukachaisiriku *et al.* 2008

(contd. table 1)

Phomopsis sp.	*Excoecaria agallocha*	-	Phomopsin A, B, and C, cytosporone B and C	Huang *et al.* 2008b
Phomopsis sp.	*Alpinia shengzhen*	Antibacterial	phomolides A and B, phomenes A–C, colletotricholide A	Rukachaisirikul *et al.* 2008
Phomopsis sp.	*Annona squamosa*	-	Lactone	Lin *et al.* 2008
Phomopsis sp.	*Azadirachta indica*	Antifungal	Lactones	Wu *et al.* 2008
Diaporthe sp.	-	cytotoxic	Phomopsolide B (122) and its derivative (123)	Yuan *et al.* 2009
Phomopsis sp.	*Camptotheca acuminate*		butanoate derivatives (139–142), furanopolyketides (143, 144) and 4-ethyltetrahydro-3-methyl-5-propylfuran-2,3-diol	Lin et al 2009
D. phaseolorum	*Espeletia* sp.	Antifungal	-	Prada et al 2009
Phomopsis sp.	*Musa acuminata*	Cytotoxic	Hexaketide γ-lactones. Oblongolides Z, and 2-deoxy-4α-hydroxyoblongolide X	Bunyapaiboonsri *et al.* 2010
Phomopsis sp.	*Excoecaria agallocha*	Cytotoxic	5-hydroxy-6,8-dimethoxy-2-benzyl-4*H*-naphtho[2,3-b]-pyran-4-one (47)	Huang *et al.* 2010
Phomopsis sp.	*Odontoglossum* sp.	Antifungal	sabinene (a monoterpene with a peppery odor), 1-butanol, 3-methyl; benzeneethanol; 1-propanol, 2-methyl, and 2-propanone	Singh et al. 2011
Phomopsis sp.	*Allamanda cathartica*	Antibacterial	terpene	Nithya & Muthumary 2011
Phomopsis sp.	*Notobasis syriaca*	Antibacterial Antifungal Algicidal	phomosine K, phomosine A, phenylalanine amide, 2-hydroxymethyl-4β,5α,6β-trihydroxycyclohex-2-en, (-)-phyllostine, (+)-epiepoxydon, and (+)-epoxydon monoacetate	Hussain *et al.* 2011

(contd. table 1)

Phomopsis sp.	*Ligustrum vulgare*	Anti-microbial	Phomosines H-J,	Krohn *et al.* 2011
P. archeri	*Vanilla albidia*	Antimalarial	Phomoarcherins A-C, and four known compounds, kampanol A, R-mevalonolactone, ergosterol, and ergosterol peroxide,	Hemtasin *et al.* 2011
Diaporthe sp.	*Pandanus amaryllifolius*	Antibacterial	diaportheones A (74) and B (75)	Bungihan *et al.* 2011
Phomopsis sp.	*Ligustrum vulgare*	-	d phomosines A–K	Krohn *et al.* 2011
Phomopsis sp. (syn. *Diaporthe* sp.)	*Musa acuminata* *Cistus monspeliensis*	-	5-(hydroxymethyl) mellein	Bunyapaiboonsri *et al.* 2010 Ahemad *et al.* 2011
D. longicolla &*D. melonis*	*Gossypium hirsutum*&*G. arboreum*	Antifungal	-	Fu *et al.* 2011
Phomopsis longicolla	*Bostrychia radicans*	Antibacterial	18-deoxycytochalasin H, mycophenolic acid, and dicerandrol C	Erbert *et al.* 2012
Phomopsis sp.	-	Antibacterial	(2R,3S)-7-ethyl-1,2,3,4-tetrahydro-2,3,8-trihydroxy-6-methoxy-3-methyl-9,10-anthracenedione (1), anthraquinones, two known phenylethyl alcohols, butanamide	Klaiklay *et al.* 2012
Phomopsis sp.	*Orthosiphon stamineous*	Antibacterial Antifungal Anticandidal	-	Tong *et al.* 2012
Phomopsis sp. PSU-D15	*Garcinia dulcis*	-	Altersolanol A	Baker & Satish 2012
Diaporthe sp.	*Cistus salvifolius*	Antifungal		Hussain et al 2012
Phomopsis sp.	-	Antifungal	phomopsinones A–D (117–120)	Hussain *et al.* 2012
Diaporthe sp.	*Endodesmia calophylloides*	Antifungal	excelsional (**1a**) and 9-hydroxyphomopsidin (**2a**), together with excelsione (**1b**), phomopsidin (**2b**), alternariol (**3a**), alternariol-5-*O*-methyl ether (**3b**), the hitherto undescribed 5'-hydroxyalternariol (**3c**), altenusin (**4,** xanthochymol (**5**) and 1,5-dihydroxy-3-methoxyxanthone (mesuaxanthone, **6**)	Talontsi *et al.* 2012
Phomopsis sp.	*Aconitum carmichaeli*	Antifungal	(14β, 22E) -9,14-dihydroxyergosta-4,7,22-triene-3,6-dione and (5α,6β,15β,22E) -6-ethoxy-5,15-dihydroxyergosta-7,22-dien-3-one, calvasterols A and B, and ganodermaside D	Wu *et al.* 2013
Phomopsis sp.	*Ficus pumila*	Anti-microbial	-	Rakshith et al.2013
Diaporthe sp.	*Camptotheca acuminata*	-	polyketide f	Liu *et al.* 2013
Phomopsis sp. cib-109.	-	-	21-acetoxy-6,7,18-trihydroxy-5,6,16,18-tetramethyl[11]cytochalasa-13,19-trans-dien-1-one (cytochalasin R1)	Zhan et al. 2013

(contd. table 1)

Phomopsis sp.	*Paris polyphylla* var. *yunnanensi*	Cytotoxicity	Xanthones, 1,5-dihydroxy-3-hydroxyethyl-6-methoxycarbonylxanthone, 1-hydroxy-5- methoxy-3-hydroxyethyl-6-methoxycarbonylxanthone, and 1-hydroxy-3-hydroxyethyl- 8-ethoxycarbonylxanthone, xan thones	Yang *et al.* 2013
P. longicolla *Phomopsis* sp.	-	-	benzopyran-4-one derivative lachnone A (71), the benzopyran-2-one derivative (72), and phomochromanone (73),	Huang *et al.* 2010; Rönsberg *et al.* 2013
Diaporthe sp.	*Rhizophora mucronata*	Antifungal	-	Shiono *et al.* 2013
D. amygdali	*Aconitum carmichaeli*	Antifungal	-	Ma *et al.* 2014
Phomopsis sp.	*Aconitum carmichaeli*	Antiviral	16-acetoxycytosporone B, dankasterone A, dankasterone B, 3β,5α,9α-trihydroxy-(22E,24R)-ergosta-7,22-dien-6-one, and cyclonerodiol oxide	Ma *et al.* 2014
D. melonis	*Annona squamosa*	Antibacterial	Dihydroanthracenone atropodiastereomers, diaporthemins A (3), B (4) & flavomannin-6,6'-dimethylether (5).	Ola *et al.* 2014
Phomopsis Sp. ED2	*Orthosiphon Stamineus*	Antimicrobial	-	Tong *et al.* 2014
P. vexans	*Solanum virginianum*	Lower blood cholesterol	lovastatin	Parthasarathy & Sathiyabama 2015
P. longicolla	*Ficus pumila*	Antibacterial	Dicerandrol C	Fouda *et al*. 2015
Phomopsis sp.	-	-	Tenuazonic acid and 3-nitropropionic acid	Jena *et al.* 2015
Phomopsis sp.	*Aconitum carmichaelii*	Anti-microbial	Cyathisterol, (24R)-6-hydroxy-24-ethylcholest-4-en-3-one, hydroxyvertixanthone, isosclerone, 7-methoxy-4,6-dimethylphthalide, convolvulol, 4-hydroxybenzaldehyde, phenylacetic acid, 1H-indole-3-carbaldehyde, 3-hydroxyindole, nicotinic acid, adenosine, N-hexadecanoylsphinganan, 9,10,11-trihydroxy-(12Z)-octadecenoic acid, 8-hydroxy-(9E)- octadecenoic acid, 1-monopalmitin, and (2E)-nonadecenoic acid	Huang *et al.* 2015
P. amygdali	-	-	xanthones (77–81)	Hu *et al.* 2015
Diaporthe sp. *LG23*	*Mahonia fortunei*	Antibacterial	9-nor-Lanosta-5(10),6,8,24-tetraene-1α,3β,12β,22S-tetraol (5); 3β,5α,9α-Trihydroxy-(22E,24 R)-ergosta-7,22-die n-6- one (6); 3β,5α,9α,14α-Tetrahydroxy-(22E,24 R)-ergosta 7,22-dien-6-one (7); (22E,24 R)-Ergosta-7,9(11),22-triene 3β,5α,6α-triol (8); Chaxine C (9); Demethylincisterol A3 (10); Volemolide (11)	Li *et al.* 2015

(contd. table 1)

Phomopsis sp.	-	Anticancerous	mycoepoxydiene	Zhu *et al.* 2015
Diaporthe sp. SNB-GSS10	*Sabicea cinerea*	Cytotoxic	Mycoepoxydiene (1); Altiloxin A (2); Enamidin (3); Eremofortin F (4)	Mandavid *et al.* 2015
P. archeri	*Vanilla albindia*	Antimalarial	sesquiterpene, phomoxanthones A-C	Aharwal *et al.* 2016
Phomopsis sp.	*Garcinia kola*	Antibacterial	18-metoxycytochalasin J, cytochalasins H and J, and alternariol	Jouda *et al.* 2016
P. theicola	*Litsea hypophaea*	Anti-inflammatory	phomocytochalasin, cytochalasin H, cytochalasin N, RKS-1778, dankasterone B, cyclo(L-Ile-L-Leu)	Hsiao *et al.* 2016
D. maritime DAOMC628553	*Picea rubens*	Antibiotic	Phomopsolides A-C (14-16); (S,E)-6-(4-hydroxy-3-oxopent-1-en-1-yl)-2 H-pyran-2-one (17)	Tanney *et al.* 2016
Phomopsis sp.	*Isodon eriocalyx* var. *laxiflora*	Cytotoxic, anti-inflammatory, and anti-migratory activities	Phomopchalasins A-C	Yan *et al.* 2016
Phomopsis sp.	Mangrove	Anticancerous	cytochalasins, Phomopsichalasins D-G,	Luo *et al.* 2016
D. maritima	*Picea* spp.	Antifungal	Phomopsolides A–C, alpha-pyrone.	Tanney *et al.* 2016
Diaporthe sp. 1308-05	*Aucuba japonica var. borealis*	Cytotoxic	Homopetasinic acid (12)	Ito *et al.* 2016
Diaporthe citri	*Mikania glomerata*	Sub-lethal	3-Nitropropionic acid (13)	Polonio *et al.* 2016
D. endophytica	*Maytenus ilicifolia*	Antifungal	-	Santos *et al.* 2016; Tonial *et al.* 2017
D. terebinthifolii	*Schinus terebinthifolius*	Antifungal	-	Santos *et al.* 2016; Tonial *et al.* 2017
Phomopsis sp.	*Brucea javanica*	Antiviral	Dothiorelones A–C and H, and cytosporones C and U	Tan *et al.* 2017
D. arengae TATW2	*Terminalia arjuna*	Antihypercholesterolemi	Methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (45); Pterin-6-carboxylic acid (46); 2,6-Ditert-butyl-4-phenol (47) Phenolics Antihypercholesterolemic hRBC (red blood cell) [1]	Patil *et al.* 2017
Phomopsis sp.	*Garcinia* spp.	Antibacterial	Phomoxanthone A, B	Kumar *et al.* 2017
Phomopsis sp. PSU-H188	*Hevea brasiliensis*	Antibacterial	cytochalasin N (25) and diaporthalasin (26)	Kongprapan *et al.* 2017
Diaporthe phaseolorum-92C	*Combretum lanceolatum*	Antiparasitic	18-des-hydroxy Cytochalasin H	Brissow *et al.* 2017
Diaporthe phaseolorum SKS019	*Acanthus ilicifolius*	Cytotoxic	Diaporphasines A-D (36-39) Meyeroguillines A, C and D (40-42); 5-Deoxybostrycoidin (43); Fusaristatin A (44)	Cui *et al.* 2017
Diaporthe toxica	*Lupinus* sp.	Hexapeptides Cytotoxi	Hexapeptides Cytotoxic	Schlob *et al.* 2017
D. miriciae UFMGCB 9720	Vellozia gigantea	antifungal, antibacterial, and antimalarial activities	- epoxycytochalasin H,	Ferreira *et al.* 2017

(contd. table 1)

Phomopsis thea	*Vitex negundo*	Anti-microbial	pyrimidine imino methylfuran derivative	Jayanthi *et al.* 2018
Phomopsis sp. (*D. miriciae*)	*Copaifera Pubiflora&Melocactus ernestii*		Cytochalasin H, N	Carvalho *et al.* 2018
Phomopsis sp.	*Phyllanthus glaucus*	hepatotoxicity	2,3-seco-protoilludane-type sesquiterpenoid, Protoilludane-type sesquiterpenoids, Illudalane-type sesquiterpenoids, Botryane-type sesquiterpenoid and sesquiterpenoids	Wu *et al.* 2018
D. pseudomangiferaea	*Tylophora ouat*	Antifibrosi Cytotoxicitc Anti-diabetic	Acetoxydothiorelones A and B (77-78); Dothiorelones K-N (79-82); 16-Acetoxydothiorelone C (83); Dothiorelones A-C (30-32); Dothiorelones G and I (84-85); Cytosporone D (35); Pestalotiopsone B (86); Mucorisocoumarin A (87); 5-Hydroxy-7-methoxy-4,6-dimethyl-2-phenylisoindoline-1,3-dione (88); Diaporphthalide A (89); Diaporlactone A (90); Xylarolide (91); Xylarolides A and B (92-93); Diportharine A 94)	Liu *et al.* 2018
Diaporthe sp.	*Datura inoxia*	Antioxident Cytotoxic	xylarolides A and B (92-93)	Sharma *et al.* 2018
Diaporthe cf.*heveae*	*Vochysia divergens&Stryphnodendron adstringens*	Antifungal	-	Noriler *et al.* 2018
Diaporthe sp.	*Pachystachys lutea*	Antifungal	-	Ribeiro *et al.* 2018
Diaporthe sp. ECN-137	*Phellodendron amurense*	Antimigration	Diaporthols A and B: b	Nakashima *et al.* 2018
Diaporthe sp. SCSIO 41011	*Rhizophora stylosa*	Cytotoxic	Isochromophilones A-F (61-66); 5-Chloroisorotiorin (67); epi-Isochromophilone (68); Isochromophilone III (69); epi-Isochromophilone III (70); 6-((1E,3E)-3,5-Dimethylhepta-1,3-dien-1-yl)-2,4- dihydroxy3-methylbenzaldehyde (71); (2E,4E)-1-(2,6-Dihydroxy-3,5-dimethylphenyl)hexa-2,4-dien-1-one (72)	Luo *et al.* 2018
Diaporthe sp.SYSU-HQ3	*Excoecaria agallocha*	Anti-tuberculosis	Diaporisoindoles A-E (49-53); Tenellones C and D (54-55); Diaporindenes A-D (56-59); Isoprenylisobenzofuran A (60)	Cui *et al.* 2018
Diaporthe sp. ARL-09	*Anoectochilus roxburghii*	Cytotoxic	Cytoskyrin C (75); Epicytoskyrin (76)	Tian *et al.* 2018
Phomopsis sp.	-	Antifungal	-	Huang *et al.* 2019
D. lithocarpus A740	*Morinda officinalis*	Cytotoxic	Tenllone I (95); Lithocarins B-D (96-98); Tenellone H (99); Phomopene (10	Liu *et al.* 2019
Diaporthe sp. GZU-1021	*Chiromanteshaematochir*	Anti-inflammatory Cytotoxic	Diaporthichalasins A-C (101-103); Phomopsichalasin G (104); 21- O-Deacetyl-L-696,474 (105); Cytochalasin H (106); Biatriosporin N (107); Phomopsichin B (108); Penialidin A (109); Phomoxanthone A (110)	Liu *et al.* 2019

(contd. table 1)

Diaporthe sp.	*Cinnamomum loureiroi*	Bactericidal Fungicidal	Eugenol	Tanapichatsakul *et al.* 2019
Phomopsis sp.	*Salvia miltiorrhiza*	Antifungal	-	Huang *et al.* 2019
Diaporthe sp. SCSIO 41011	Mangrove	-	chloroazaphilones (isochromophilones A-F, (61-66)	Luo *et al.* 2019
Diapothe vochysiae	*Vochysia divergens*	Atibacterial Cytotoxic	Vochysiamides A and B (111 - 112); 2,5-Dihydroxybenzyl alcohol (113)	Noriler *et al.* 2019
Phomopsis sp.	*Smallanthus sonchifolius* *Viguiera arenaria*	Antimalaria/Antiparasite	Stemphyperylenol 3,4-dimethyl-2-(40-hydroxy-30,50-dimethoxyphenyl)-5-methoxy-tetrahydrofuran	Caruso *et al.* 2020
Phomopsis sp. CFS42	*Cephalotaxus fortunei*	Antifungal	Phomotide A (114); 4 -Acetyl-3,4-dihydro-6,8-dihydroxy3-methoxy-5-methylisocoumarin (115)	Ma *et al.* 2020
Phomopsis sp.	*Achyranthes bidentata*	Cytotoxicity	Phomopsones A-C, Azaphilones	Yang *et al.* 2020
Diaporthe eucalyptorum KY-9	*Melia azedarach*	Antifungal	Eucalyptacid A (116); Eucalactam B (117); Eugenitol (118);Cytosporone C (119); 4-Hydroxyphenethyl alcohol (120); 1-(4-Hydroxyphenyl)ethane-1,2-diol (121); N-(2-Hydroxy-2-phenylethyl)acetamide (122); Phomopene (100)	Gao *et al.* 2020
P. asparagi	*Rhizophora mangle*	Immunosuppressive	diaporchromone A, C and D, phomochromenones C–F	Wei *et al.* 2021
D. phragmatis (syn. *D. eres)*	*Actinidia chinensis*	Antimicrobial	-	Yu *et al.* 2021
Diaporthe terebinthifolii CMRP1430 & CMRP1436	*Schinus terebinthifolius*	Antimicrobial	-	dos Santos *et al.* 2021
Diaporthe eres (SPEF004)	*Ligustrum obtusifolium.*	Antibacterial Cytotoxic Antidiabetic	-	Saravanakumar *et al.* 2021
D. phaseolorum	*Solanum lycopersicum*	-	-	Rashid *et al.* 2021
Diaporthe sp. SCSIO 41011	Mangrove	HIV latency-reversal and anti-influenza A virus activities.	1-methoxypestabacillin B (**1**), sesquiterpenoid (**2**), chrodrimanin-type meroterpenoids (**3**? **8**)	Luo et al. 2021
Phomopsis sp.	*Alpinia shengzhen*	Cytotoxic Antibacterial	sesquiterpenoids, phomenes A–C, phomolides A and B, colletotricholide A	Chen *et al.* 2022
D. eres	*Prunus domestica*	Antifungal	-	Abramczyk *et al.* 2022
Phomopsis sp.	*Passovia stelis*	Antilarvidal	3-nitropropionic acid	Garcia 2022
D. foeniculina	*Balanophora polyandra*	Antibacterial	-	Wu *et al.* 2022
Phomopsis sp. shj2	-	Antimigration activity	cytochalasin H (8), cytochalasin J1 (9), RKS-1778 (10), and 21-acetoxycytochalasin J2 (11),	Yan et al. 2022
Phomopsis sp.	*Rhizophora mangle*	Cytotoxic	Isocoumarins and Pyrone derivative	Guo *et al.* 2023
Diaporthe sp. AC1	*Artemisia argyi*	Antibacterial	-	Zhang *et al.* 2023
D. unshiuensis YSP3	*Caesalpinia sepiaria*	cytotoxic bactericidal	phomopthane A and B, **1** and **2, ,**alternariol methyl ether derivative (**3**), phomopyrone B, **4**	Khan *et al.* 2023
Diaporthe biguttusis T-24	*Ligularia fischeri*	Cytotoxic	Diaporthpyran A (**1**), diaporthester E (**2**) and diaporthester F (**3**)	He *et al.* 2023
Diaporthe caliensis	*Otoba gracilipes*	Antimicrobial	phomol (**1**), aliensolides A (**2**) and B (**3**)	Charria-Girón *et al.* 2023

2005). Similar conclusions were subsequently reported by several other research groups ((Murali *et al.* 2006; Chaeprasert *et al.* 2010; Sun *et al.* 2011; Udayanga*et al.* 2011). Isolates of *Phomopsis* in various studies confirmed the ambiguity in distinguishing them from one another due to their similarity in morphological characteristics (Shenoy *et al.* 2007). Numerous studies (Pandey *et al.* 2003; Jeewon *et al.* 2004; Murali *et al.* 2006; Sieber 2007; Udagaya *et al.* 2011; Wikee *et al.* 2011) have suggested that some endophytic genera, such as *Phomopsis*, including *Colletotrichum, Phoma,* and *Phyllosticta*, have a broad host range and colonize several taxonomically unrelated plant hosts. The examination of literary works reveals the presence of *Phomopsis* as an endophyte in nearly every host investigated for endophytic fungus.Johnson *et al.* (1992) reported *P. mangiferae* to be endophytic in mango stem tissue; Petrini and Fisher (1990) found a high incidence of *P. salicina* and an unnamed *Phomopsis* sp. in shoots of willow (*Salix fragilis*) and oak (*Quercus robur*), respectively. Bissegger and Sieber (1994) discovered that one of the four most commonly isolated endophytic species from chestnut coppice shoots (*Castanea sativa*) was an unidentified *Phomopsis* sp. Based on these reports, the genus *Phomopsis* appears well-suited for an endophytic role. Promputtha *et al.* (2007) isolated 24 *Diaporthe* (as *Phomopsis*) species from 31 morphospecies of sterile *Magnolia liliflora* (*Magnoliaceae*) endophytes. Similarly, Luo *et al.* (2022) isolated 12 endophytic species *Diaporthe* species from a traditional medicinal plant in China. Huang *et al.* (2008) reported *Diaporthe* as one of the dominant endophytes on *Allamanda catharitica*, *Alstonia scholaris*, and other 29 traditional Chinese medicinal plants.

This suggests that they have evolved adaptations to withstand various host defenses. The host specificity of this genus is disputed, as indicated by the research on 11 *Phomopsis* isolates from the teak trees of moist and dry deciduous forests of the Nilgiri Biosphere Reserve (Murali *et al.* 2006).Studies have revealed that there are not many seasonal variations in the dominance of this genus for a given host plant. Jayanthi *et al.* (2014) reported frequently isolated and dominant genera, irrespective of the season, were *Phomopsis* (*Phomopsis arnoldiae*, *P. stipata*, *P. tersa*, and *Phomopsis* sp.) from leaves and stems of *Anisomeles malabarica*,during all seasons. Washington *et al.* (1999) isolated the endophyte *Phomopsis castanea* (Sacc.) from seeds. However, *Phomopsis* nut rot, a significant post-harvest disease, is associated with *P. castanea*. When seemingly healthy plants of four cultivars were sampled over a year, it was also discovered that the fungus occurred endophytically in the plant parts of European chestnuts, including leaves, shoots, flowers, and fruits. *Phomopsis liquidambaris* was first reported as an endophyte from healthy living branches of *Liquidambar formosana* (Hamamelidaceae) in Fujian Province, China (Chang-Qing *et al.* 2005).

Role of Diaporthe endophyte in drug discovery

Diaporthe is well-known for its structurally distinct and biologically active secondary metabolites (Nagarajan *et al.* 2021; Jiang *et al.* 2023). *Diaporthe* species have been widely studied for their ability to produce significant chemicals with diverse bioactivities, owing to their prevalence as endophytes and their capacity to synthesize secondary metabolites (Abramczyk *et al* 2022). Xu *et al.* (2021) compiled a total of 335 bioactive secondary metabolites isolated from species of *Diaporthe* and *Phomopsis*-like species. Some of them are also potent antiviral, antibacterial, antifungal, and algicidal cytotoxic, antibiotic, antioxidant, antimalarial, herbicidal and enzyme inhibitory compounds, which are evaluated for their *in vitro* or *in vivo* efficacies (Horn *et al.* 1994, Krohn *et al.* 1995; Horn *et al.* 1995;Isaka *et al.* 2001; Kobayashi *et al.* 2003; Elsaesser *et al.* 2005; Dai *et al.* 2005; Guo *et al.* 2023). Many bioactive metabolites with their potential are produced by endophytic *Diaporthe*/*Phomopsis* isolated from various hosts (Table1). Ma *et al.* (2014) isolated a new compound, 16-acetoxycytosporone B, along with four known compounds, viz, dankasterone A, dankasterone B, 3â,5á,9á-trihydroxy (22*E*,24*R*)-ergosta-7,22-dien-6-one, and cyclonerodiol oxide from *Phomopsis* sp. isolated from *Aconitum carmichaeli.* Among these, compound dankasterone A exhibited significant inhibitory

activity against influenza A/Thailand/Kan353/2004(H5N1) pseudovirus with an IC_{50} value of 3.56 *i*M. Compounds 16-acetoxycytosporone B, dankasterone A, and 3â, 5á, 9á-trihydroxy (22*E*, 24R)-ergosta-7, 22-dien-6-oneshowed antifungal activities against four pathogenic fungi.

The secondary metabolite (terpene) obtained from the *Phomopsis* sp. of *Allamanda cathartica* inhibited the growth of human pathogenic bacteria. The compound was extracted with organic solvents, and a bioautogram was performed to check the antibacterial activity of compunds (Nithya and Muthumary, 2011). Jayanthi *et al.* (2018) isolated endophytic fungi from five medicinal plants. *Phomopsis theae* isolated from *Vitex negundo* in Tamil Nadu showed excellent anti-microbial activity against *Pseudomonas aeroginosa, Staphylococcus aureus,* and *Candida albicans*. A novel antibacterial and anticandidal molecule was isolated from the crude ethyl acetate extract of *Phomopsis theae* using bioassay-guided fractionation. This substance was subsequently identified as a pyrimidine imino methylfuran derivative.

Even at extremely low concentrations (5 μg/mL), this drug had strong antibacterial activity against *S. aureus, P. aeroginosa,* and *C. albicans*; the minimum inhibitory concentration (MIC) was determined to be 1.25 μg/mL against all pathogens. Consequently, the data obtained firmly implies that *Diaporthe* may be a viable option for developing novel antibiotics. Jouda *et al.* (2016) isolated and elucidated the structure of antibacterial and cytotoxic compounds from *Phomopsis* sp., inhabiting *Garcinia kola* nuts. A crude extract was prepared by using the mycelium of *Phomopsis* sp. Three already known cytochalasins, namely 18-metoxycytochalasin J, cytochalasins H and J, and alternariol, were obtained through the fractionation of the crude extract. The antibacterial activities of the isolated compounds were assessed using the broth microdilution method, and for anti-cancer testing, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide techniques were used. The hemolytic properties of the sample were also examined spectrophoto-metrically against human red blood cells. The cytochalasin compounds demonstrated various levels of antibacterial activity against the tested bacterial pathogens. The most resistant microorganisms were *Vibrio cholerae* PC2 and SG24, while the most sensitive was *Shigella flexneri*. Even at a dose of up to 512 μg/mL, ampicillin exhibited no antibacterial action against *Shigella flexneri*, *Vibrio cholerae* NB2, or *V. cholerae* PC2. Interestingly, however, these multidrug-resistant bacterial strains were susceptible to the metabolites of cytochalasin. Additionally, these substances had strong cytotoxic effects on human cancer cells (LC50 = 3.66–35.69 μg/mL) while remaining less harmful to healthy non-cancerous cells. *Phomopsis* sp. PSU-D15 isolated from the *Garcinia dulcis* plant can synthesize the bioactive metabolites phenolamide and phospho-nitroester, which can inhibit *Mycobacterium tuberculosis* H37Ra at a minimum inhibitory concentration (MIC) of 6.25 μg/ml (Rukachaisirikul *et al.* 2008). Two new steroids, (14â, 22E)9,14-dihydroxyergosta-4,7,22-triene-3,6-dione and (5á,6â,15â,22E)-6-ethoxy-5,15-dihydroxyergosta-7,22-dien-3-one, together with three known steroids, calvasterols A and B, and ganodermaside D from the broth culture of *Phomopsis* were isolated from *Aconitum carmichaeli* (Wu *et al.* 2013). Further characterization of these compounds and in vitro antifungal effects were elucidated for these compounds in the broth dilution method. These compounds showed weak to moderate antifungal activity (Wu *et al.* 2013).

One new compound [tetrahydroanthraquinone derivative (2R,3S)-7-ethyl-1,2,3,4-tetrahydro-2,3,8-trihydroxy-6-methoxy-3-methyl-9,10-anthracenedione],along with five known anthraquinones, two known phenylethyl alcohols, and one known butanamide were isolated from *Diaporthe* sp. *Phomopsis* sp. PSU-MA214, inhabiting mangroves. (2R, 3S)-7-ethyl-1,2,3,4-tetrahydro-2,3,8-trihydroxy-6-methoxy-3-methyl-9,10-anthracenedione,a rare ethyltetrahydro anthraquinone, had modest antibacterial activity against methicillin-resistant *S. aureus* SK1 and standard *S. aureus* ATCC25923 as well as mild cytotoxicity against breast cancer (MCF-7) cell lines (Klaiklay *et al.* 2012). In 2011, Hussain *et al.* reported the discovery of Phomosine K, a new phomosine derivative, along with six other known compounds from *Phomopsis* sp. isolated from *Notobasis syriaca:* phomosine A, phenylalanine

amide, 2-hydroxymethyl-4â,5á,6â-trihydroxy-cyclohex-2-en, (-)-phyllostine, (+)-epiepoxydon, and (+)-epoxydon monoacetate. Phomosine K was found to have substantial antibacterial activity in preliminary investigations, while (-)-phyllostine and (+)-epoxydon monoacetate demonstrated good antifungal, antibacterial, and algicidal characteristics.

Wei *et al.* (2021) isolated four novel chromones, phomochromenones D–G, from the culture of *Phomopsis asparagi* DHS–48, isolated from Chinese mangrove *Rhizophora mangle*, together with four known counterparts, diaporchromone A, diaporchromanone C, diaporchromanone D, and phomochromenone C. The absolute configurations of phomochromenones D and phomochromenones G were determined using a modified Mosher's technique and fundamental hydrolysis. Diaporchromone A had a moderate to mild immunosuppressive effect against T and/or B lymphocyte cells, with IC_{50} values of 34 μM and 117 ìM, respectively. Diaporchromone A had an IC_{50} of 34 μM and 117 μM, respectively, and demonstrated moderate to mild immuno suppressive action against T and/or B lymphocyte cells. Chen *et al*. (2022)reported the presence of three new sesquiterpenoids (phomenes A–C), two previously unidentified lactones (phomolides A and B), and one known chemical (colletotricholide A) from *Phomopsis* sp. They evaluated the cytotoxic and antibacterial activities of compounds. They demonstrated that phomolides B showed potent antibacterial inhibition against methicillin-resistant *S. aureus* and *S. aureus* with a minimum inhibitory concentration as low as 6.25 mg/ml, comparable to the clinical drug vancomycin. Horn *et al.* (1995) isolated the anti-microbial compound phomopsichalasin from *Phomopsis* sp., fermented on shredded wheat. It was active against pathogenic *Bacillus, Staphylococcus*, *Salmonella*, and C*andida.* Similarly, compounds Phomoxanthone A and Phomoxanthone B were isolated from *Phomopsis* sp. and exhibited significant activity against *Mycobacterium tuberculosis* (Isaka *et al.* 2001). Antibacterial dicerandrols A–C were isolated from *Phomopsis longicolla*, inhabiting *Dicerandra frutescens* (Wagenaar and Clardy ,2001).

Phomopsis theicola was isolated from *Litsea hypophaea* Hayata*,* a plant that is endemic to Taiwan(Hsiao *et al.* 2016). They isolated phomocytochalasin (a new cytochalasin), cytochalasin H, cytochalasin N, RKS-1778, dankasterone B, and cyclo (L-Ile-L-Leu) from the solid state fermentation with *Phomopsis theicola*. From the isolated compounds, Cytochalasin H showed progesterone receptor (PR) antagonism with the IC_{50} value of 1.42 μM compared with positive control RU486 (IC_{50} values 0.063 nM) and cytochalasin N exhibited no inhibitory activity with IC_{50} values of 77.8 ìM compared to quercetin (IC_{50} value 36.8±1.3μM), which was used as positive control in this study. Seaweed-derived fungi have proven to be a plentiful source of secondary metabolites with unique structural characteristics and biological activity (Bugni and Ireland, 2004). Huang *et al.* (2008b) identified three unknown metabolites, Thompson A-C, and two known compounds, cyclosporine B-C, from *Phomopsis* sp. found in the South China Sea mangrove plant *Excoecaria agallocha.*

A strain of *Phomopsis* sp. was isolated from the fresh leaves of *Alpinia shengzhen*, a horticultural plant of Zingiberaceae (Rukachaisirikul *et al.* 2008). Together with one known molecule, colletotricholide A, they have identified three novel sesquiterpenoids, phomenes A–C, and two previously undescribed lactones, phomolides A and B. Phomolides B, demonstrated appreciable antibacterial activity against methicillin-resistant *Staphylococcus aureus* and strains of *S. aureus* with a minimum inhibitory concentration as low as 6.25 mg/ml, which was equivalent to the clinical drug vancomycin (Rukachaisirikul *et al.* 2008). The potential role of endophytes in protecting plants from fungal diseases such as Dutch elm disease has been explored (Brayford 1990). *Phomopsis* sp. from the living bark of *Cavendishia pubescens* in Colombia produced paspalitrem A and paspalitrem C in batch fermentations (Bills *et al.* 1992). Thus, the presence of endophytes in plants may be advantageous (Hyde and Soytong ,2008; Weber 2009; Vesterlund *et al.* 2011). The study by Hilario and Goncalves (2022) also suggests that species of this genus have potential as biofertilizers, given their ability to promote plant growth and enhance stress tolerance.

Anti-microbial Activities

Several reports suggest the potential of the genus *Phomopsis* to produce numerous bioactive compounds. Reports also indicate that many of these compounds possess significant anti-microbial activities *in vitro* (Rukachaisirikul *et al.* 2008; Xu *et al.* 2019; Chen *et al.* 2020; Liu *et al.* 2021). Metabolites, identified as phomoenamide, phomonitroester, and deacetylphomoxanthone B, were extracted from the *Phomopsis* sp. along with three other dicerandrol A, (1S, 2S,4S)-p-menthane-1,2,4-triol, and uridine. The in vitro antimycobacterial activity of homoenamide against *M. tuberculosis* H37Ra has been reported to be moderate. Metabolite from *Phomopsis* sp. PSU-D15 exhibited a MIC value of 6.25 μg/ml and moderate in vitro antimycobacterial activity against *Mycobacterium* TB H37Ra (Rukachaisirikul *et al.* 2008). Erbert *et al.* (2012) studied the red seaweed *Bostrychia radicans* for their endophytic assemblages and their molecularly diverse and biologically active natural chemical products. *Phomopsis longicolla* was found to produce dicerandrol C that had significant anti-microbial activity against *S. aureus* (ATCC 6538) and *S. saprophyticus* (ATCC 15305), with minimum inhibitory concentrations of 1 and 2 μg ml^{-1}, respectively. These findings demonstrate the existence of exciting metabolites and suggest that these organic compounds should be considered while creating novel antibiotics. *Phomopsis* sp., isolated from the stem of *Azadirachta indica* by Wu *et al*. (2008), isolated one 10-membered lactone showed antifungal activity in the MIC value range of 31.25–500 μg/mL. Dicerandrol C from *P. longicolla* also exhibits antibacterial activity against *S. aureus* and *S. saprophyticus* (Rafael *et al.* 2015). Endophytic *Phomopsis* sp. isolated from the stem of *Ficus pumila* had excellent antibacterial activity against Gram-positive and Gram-negative human and phytopathogenic bacteria (Fouda *et al.* 2015).

Tenuazonic acid from *Phomopsis* sp. has shown potential as an anti-microbial agent against *M. tuberculosis* by altering the pathway of isocitrate lyase enzymes (Jena *et al.* 2015). Species of *Phomopsis* isolated from *Spondias mombin* and *Aspidosperma tomentosum* were tested for their antibacterial activity. Three of the 13 extracts effectively inhibited the growth of all test organisms (Corrado and Rodrigues, 2004). Tong *et al*. (2012) tested ethyl acetate, hexane, dichloromethane, and butanol extracts of *Phomopsis* sp. ED2 was isolated from the flowers of the *Orthosiphon stamineous* Benth for their antibacterial, antifungal, and anticandidal activities and recorded that endophytic *Phomopsis* sp. is a potential source of novel chemotherapeutic agents. Phomoxanthone A and phomoxanthone B were extracted from *Phomopsis* sp. from Thailand and exhibited significant activity against *M. tuberculosis* (Isaka *et al.* 2001). Antibacterial dicerandrols A–C were isolated from *P. longicolla,* an endophyte of *Dicerandra frutescens* (Wagenaar and Clardy 2001). Nectriapyone, effective against *S. aureus*, was isolated as an antibiotic from the fungus *Gyrostroma missouriense* (Seeler) (Nair & Carey 1975). The endophytic fungi *Phomopsis oblonga* (Claydon *et al.* 1985) and *Gliocladium vermoesenii* (Avent *et al.* 1991) also biosynthesize nectriapyrone; novel antibiotic, phomol, isolated from *Phomopsis* species. Another two anti-microbial compounds, cytosporone B and C, were isolated from the same genus, *Phomopsis* sp. They inhibited two pathogens, C*. albicans,* and *F. oxysporum,* with MIC values ranging from 32 to 64 mg/ml. Dhakshinamoorthy *et al.* (2021)were the first to screen, isolate, and analyse the antibacterial assays of Camptothecin (CPT) and derivatives from the endophytic fungus *Diaporthe caatingaensis* of *Buchanania axillaris,* a plant collected from Sathyamangalam Tiger Reserve forest, Tamil Nadu. They recorded the maximum yield of 0.681 mg/L of CPT by the fungus *D. caatingaensis* and their antibacterial potential with 12.5–25 μg/ml MIC.

In an investigation of endophytic *Phomopsis cassia,* ethyl 2,4-dihydroxy-5,6-dimethylbenzoate, and phomopsilactone displayed strong antifungal activity against two phytopathogenic fungi, *Cladosporium cladosporioides* and *C. sphaerospermum* (Weber *et al.* 2004, Silva *et al.* 2005, Huang *et al.* 2008). *Phomopsis* sp., isolated from *Musa acuminata*, produced 2-deoxy-4á-hydroxyoblongolide X and hexaketide ã-lactones. Oblongolides Z showed antiherpes simplex virus type 1 (HSV-1) activity with IC_{50} values of 14 μM and 76 μM, respectively. Oblongolides Z exhibited comparable cytotoxic activity against KB, BC, NCI-H187, and nonmalignant Vero cell lines with

IC_{50} values of 37, 26, 32, and 60 μM, respectively (Bunyapaiboonsri *et al.* 2010). Singh *et al.* (2011) reported a unique mixture of volatile organic compounds (VOCs), including sabinene (a monoterpene with a peppery odor), 1-butanol, 3-methyl, benzene-ethanol, 1-propanol, 2-methyl, and 2-propanone from *Phomopsis* sp., which was isolated as an endophyte of *Odontoglossum* sp.(Orchidaceae). An artificial mixture of VOCs mimicked the antibiotic effects of *Phomopsis* sp. with remarkable bioactivity against a variety of plant pathogenic test fungi, including *Phytophthora, Pythium, Rhizoctonia, Sclerotinia, Botrytis, Fusarium, Verticillium*, and *Colleto-trichum. Phomopsis* sp. gases have also been found to have antifungal properties.

Phomopsis sp. was identified from *Cavendishia pubescens*, a woody host, in Colombia. Paspalitrems A and C were found to be produced by the fungus. At the time, Bills *et al.* (1992) reported that these chemicals were only known to be formed from the sclerotia of *Claviceps paspali*, which caused neurological problems in animals. Xie*et al.* (2017) tried to investigate the biological control of *Fusarium solani* in soil enriched with phenolic acids by inoculating the endophytic fungus *Phomopsis liquidambari*, as the increase of soil-borne pathogens induced by phenolic acids that accumulate in continuous cropping soil reduces the yield and quality of crops. They confirmed the utilization of *P. liquidambari* in controlling *F. solani* in phenolic acid-rich continuous cropping soils.

Anti-cancer and cytotoxic metabolites

Cancer is a class of diseases defined by the progression of abnormal cell growth that can eventually infiltrate or spread to other sections of the body and cause death (Pimentel *et al.* 2010). Combinations of chemotherapy, surgery, radiation therapy, monoclonal antibodies, and immunotherapy are used in modern cancer treatments. These methods have several adverse effects, the most common of which is non-specific anti-cancer medication cytotoxicity (Gangadevi and Muthumary 2008). The cancer death rate is steadily rising even though there are many different treatment options available. This shows that the available cancer treatments are insufficient, and it may be necessary to look into more recent sources to find more targeted cancer treatment methods.

Fungi related to mangroves are valuable for finding novel bioactive natural compounds. Guo *et al.* (2023) isolated *Phomopsis* sp. from the root of the mangrove plant *Rhizophora mangle*. They isolated three new isocoumarins and one new pyrone derivative from the ethyl acetate extract of the fermentation broth of *Phomopsis* sp. Isocoumarins 1 and 3 **s**howed cytotoxic activity against HeLa cells with IC_{50} values of 11.49 ± 1.64 μM and 8.70 ± 0.94 μM, respectively; pyrone derivative exhibited cytotoxic activities against human hepatoma cells (HepG2) with an IC_{50} value of 34.10 ± 2.92 μM.

Cytochalasins are the major secondary metabolites of the genus *Phomopsis*. Luo *et al.* (2016) isolated four new cytochalasins xy22, phomopsichalasins D-G, and six known analogs from mangrove fungal endophytes, *Phomopsis* spp. xy21 and xy22. Phomopsichalasin G exhibited cytotoxic activities against HCT-8, HCT-8/T, A549, MDA-MB-231, and A2780 cancer cell lines with IC_{50} values of 7.5, 8.6, 6.4, 3.4, and 7.1 μM, respectively. A new naphtho-ã-pyrone compound, 5-hydroxy-6, 8-dimethoxy-2-benzyl-4H-naphtho [2,3-b]-pyran-4-one, obtained from *Phomopsis* sp. ZSU-H26 of the mangrove tree *Excoecaria agallocha*. This compound showed cytotoxic activity against HEp-2 (IC_{50} = 10 μg/mL) and HepG2 (IC_{50} = 8 μg/mL) (Huang *et al.* 2008). Khan *et al.* 2023 isolated *Diaporthe unshiuensis* YSP3 from the leaves of *Caesalpinia sepiaria and* elucidated the structures of two new xanthone derivatives (1 and 2), one new alternariol derivative (3), and one new pyrone derivative (4), along with eight known compounds (5–12) isolated from it. All new compounds were evaluated for their antifungal, antibacterial, and cytotoxic activities. Compound **1** revealed potent cytotoxic potencies against human cancer cell lines HeLa and MCF-7, while compound 3 showed a bactericidal effect on *B. subtilis.*

Antilarvicidal Activity

Aedes aegypti (Linnaeus 1762, Diptera: Culicidae) is responsible for the transmission of the Zika, Chikungunya, yellow fever, and dengue viruses, all of which are causes for concern in

health sectors around the world. Compound 3-nitropropionic acid from the *Phomopsis* sp. isolated from *Passovia stelis* (L.) Kuijt shows anti-larvicidal efficacy against the mosquito larvae of *Aedes aegypti*. The results of the larvicidal bioassays with 3-NPA indicated an LC_{50} of 15.172 ppm and an LC_{90} of 18.178 ppm against third-stage larvae of *Aedes aegypti* (Garcia, 2022)

Plant Protection

Insecticidal

The role of endophytic fungi in protecting the plant from insects was elucidated back in 1981 by Webber. As per his statement, the endophyte *Phomopsis oblonga* protected elm trees by generating toxic substances that counteracted the beetle *Physocnemum brevilineum*, which was the carrier of *Ceratocystis ulmi*, the agent responsible for elm Dutch disease.

Biotransformation

Phomopsis sp. isolated from *Viguiera arenaria* can biotransform tetrahydrofuran lignin to "3, 4-dimethyl-2- (4-hydroxy-3, 5-dimethoxyphenyl)-5-methoxy-tetrahydro-furan," and this compound has trypanocidal activity towards Chagas disease (Pimentel*et al.* 2011). *Phomopsis* sp. inhibited *E. hirae*, *Salmonella typhi*, *M. luteus,* and *Dothideomycetes* sp., and G8-25 inhibited *E. hirae* and *M. luteus.* Chen *et al.* (2013) demonstrated the utilization of *Phomopsis liquidambari* to eradicate environmental pollutants named Indole.

Bioremediation

Endophytes are essential for host plants to adapt to a polluted environment (Khan *et al.* 2014). Numerous endophytic microorganisms able to degrade pollutants have been successfully isolated from various plants (Sun *et al.* 2014, Zhu *et al.* 2016). *Phomopsis liquidambari* is one such fungus that has been associated with the plant *Bischofia polycarpa* for its entire life or some time. It can also survive in contaminated soil (Yan*et al.* 2011). Phenanthrene is a polycyclic aromatic hydrocarbon that is made up of three fused benzene rings. Removing it from the soil is crucial because of the significant health concerns associated with high concentrations of this organic contaminant. Tian *et al.* (2007) confirmed phenanthrene degradation by endophytic *Phomopsis* sp. (B3) singly and when co-cultured with paddy rice. When endophytic strain B3 was co-cultured with paddy rice, the degradation rate of phenanthrene was boosted when the concentration of phenanthrene was only 8.40% of that of the control after 30 days. Furthermore, it was noted that B3 lessened rice damage when phenanthrene stress was present.

Wang *et al.* (2021) isolated a strain of *Phomopsis* sp.from *Psidium guajava* grown in Nanning City, south China, and investigated their bioremediation in liquid medium as well as in soils. MCPA(2-methyl-4-chlorophenoxyacetic *acid)* is a phenoxy acid herbicide used to control broad-leaf weeds in agricultural sectors. MCPA has been frequently detected in surface water, groundwater, and well water in many countries as it is relatively soluble in water and weakly sorbed by soil, where it is highly mobile in soil (Wang *et al.* 2021). Penoxy acid herbicides could cause endocrine disturbance in humans and animals, although they have relatively slight toxicity (Bukowska *et al.* 2008, Salvo *et al.* 2015). *Phomopsis* sp. was found to be effectively degrading MCPA in contained soils. Xie and Dai (2015) demonstrated that by producing ferulic acid decarboxylase, laccase, and protocatechuate 3, 4-dioxygenase, endophytic *Phomopsis liquidambari* can degrade methoxyphenolic and ferulic acid contaminants.

Plant Growth Promotion

Endophytic fungi can synthesize medicinally useful natural chemicals unique to their host plants. This has led to the characterization and optimization of numerous fungi with these qualities for the improved synthesis of particular compounds. Endophytic *Diaporthe* species are reported as producing antimicrobial compounds to control plant pathogens, and as promising agents in the development of biofertilizers to promote plant growth (Abramczyk *et al.* 2022).

Despite this, prospective endophytic fungi's intrinsic plant colonization ability is least studied. It is beneficial to introduce advantageous traits to non-host plants by making use of the

transgenome functioning of endophytic fungi. Chithra *et al.* (2017) isolated *Phomopsis* sp. from *Piper nigrum*. HPLC and LCMS/MS confirmed the presence of piperine production in *Phomopsis* sp.

Further, the fungal isolate was screened for its colonization ability in *Oryza sativa*. Remarkably, compared to the control, the fungus-treated plants showed a notable increase in plant growth. The presence of piperine was confirmed by using the extract from treated plants. The finding obtained is highly noteworthy as it presents new opportunities for using endophytic fungal colonization in various taxonomically varied plant species (Chithra *et al.* 2017).

Species of the genus *Diaporthe* are well-recognised as promising candidates for the development of biofertilizers due to their plant growth-promoting properties. The symbiotic interactions established by fungal endophytes with host plants benefit both parties' growth. However, the genetic response of plants that drives endophyte colonization is poorly understood. *Phomopsis liquidambaris* generally supports biotic and abiotic stress resistance while existing as an endophyte in various asymptomatic hosts. Zhou *et al.* (2022) showed that *P. liquidambaris* promotes rice growth in a hydroponic system free of other microorganisms under low nitrogen conditions. Furthermore, the application of the endophytic fungus *P. liquidambari*s was found to be responsible for increased peanut yields, nodulation, and N_2 fixation (Xie *et al.* 2017). Generalist endophyte *P. liquidambaris* (syn. *D. liquidambaris),* living symbiotically with rice and peanut in their roots, was found to enhance tolerance to abiotic stress and promote plant growth (Du *et al.* 2022; Yuan *et al.* 2007). Moreover, it has been shown to induce resistance in rice against *Fusarium graminearum*, the pathogen responsible for rice spikelet rot disease (Zhou *et al.* 2022).

Additional uses of *Diaporthe* species in agriculture have been brought to light by recent research. After inoculating the hybrid *Triticum durum* × *Hordeum chilense* with a strain of *Diaporthe* sp., Aldana *et al*. 2021). They found a noteworthy increase in root and shoot biomass of up to 30%. Increased levels of vital nutrients such as calcium, magnesium, sulphur, iron, and boron were also brought about by this inoculation. Additionally, *Diaporthe* sp. strain EB4 inoculation increased proline, gibberellins, and indole-3-acetic acid levels under salt stress, which improved nutrient uptake in roots and eventually aided in plant growth (Toghueo *et al.* 2022). Furthermore, inoculating *Noccaea goesingensis* with *Diaporthe eres* enhanced plant biomass and promoted nickel accumulation, according to Wazny *et al.* 2021. This discovery establishes *D. eres* as a viable option for biofertilizer and metal-contaminated soil bioremediation.

Enzyme production

Endophytes are well known for their industrially important enzyme production with vast application range (Fouda *et al.* 2015).Several endophytic taxa, like the endophytic *Phomopsis archeri*, have demonstrated their encouraging potential for use in biotechnological processes that produce pectinases, cellulases, xylanases, and proteases (Bezerra *et al.* 2012). Also, *Phomopsis* sp. has been reported as a laccase enzyme producer (Dai *et al.* 2010). Kumar and Prasher (2021) reported significant lignolytic enzyme production in *Diaporthe phaseolorum.*

Toxic effect

As Rodrigues (1996) reported, few studies have been carried out on the effects of fungus-host interactions in tropical regions. The toxic effects of endophytes in livestock are concerned with trichothecene toxins produced by *Phomopsis* spp. strains isolated from *Baccharis* sp.in Brazil (Jarvis *et al.* 1991). The endophytic *Phomopsis* sp. HCCB03520 (*Diaporthe*) is also reported to have phytotoxic effects on the germination and radicle growth of *Medicago sativa* L., *Trifolium hybridum* L., and *Buchloe dactyloides* due to phytotoxins cytochalasins (H, N, and epoxycytochalasin H), herbaria (I and II), and a nonenolide compound (Yang *et al.* 2012).

CONCLUSION

The secondary metabolites from various host species have strong bioactivities that can aid in future medication development and innovation. The natural compounds derived from the

Diaporthe (*Phomopsis*) species exhibited a wide range of biological activity, such as antifungal, antibacterial, and anti-cancer properties. Metabolites isolated from *Diaporthe*have diverse applications in bioremediation, plant growth promotion, and biotransformation of toxic compounds. Thus, the fungal genus *Diaporthe* has broad research prospects in the future. Prospects of any form of research, including bioactivity-guided fractionation and characterization of novel chemicals isolated from *Diaporthe,* would be of great importance. Compounds isolated from this genus might soon become a very potent source of anti-cancer or anti-microbial drugs. Sophisticated and advanced research in as novel lead molecules open new avenues in drug discovery and biology.

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DECLARATION

Conflict of Interest. Authors declare no conflict of interest.

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