Endophytic fungi: a reservoir of antibacterials

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INTRODUCTION

The last two decades have witnessed a rise in the numbers of Methicillin resistant Staphylococcus aureus (MRSA), Vancomycin resistant Enterococcus faecium (VRE) and Penicillin resistant Streptococcus pneumonia (PRSP), to a variety of antibiotics (Menichetti, 2005). New drugs such as Linezolid and Daptomycin have already acquired resistance (Mutnick et al., 2003; Skiest, 2006). MDR- and XDR-TB (Gillespie, 2002; LoBue, 2009) have already acquired resistance (Mutnick et al., 2003; Skiest, 2006). Emerging global threats, being difficult to diagnose, expensive to treat and with variable results. Rice (2008) reported that the ESKAPE organism's E. faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa, and Enterobacter species are the main causative agents of infections in a majority of US hospitals. To combat all these continuing developments, a search for new and novel drugs scaffolds remains the high priority activity.

Eighty five years after the discovery of Penicillin in 1929, scientists all over the world continue to investigate natural products. The novelty of structures and scaffolds, their varied bioactivities plus their abilities to act as lead molecules is immense. According to Newman and Cragg (2012), in the years 1981–2010, ~50% of all small molecules originated from natural products. Mainly antibacterial, anticancer, antiviral and antifungals compounds from natural sources such as plant, fungi and bacteria themselves. The extraordinary advantages of natural products as sources of biotherapeutics is beyond question.

Though diverse chemical compounds with equally diverse scaffolds and bioactivities have been reported from fungi over the years, the vast group still remains to be fully exploited. Out of ~1 million different fungal species only ~100,000 have been described (Hawksworth and Rossman, 1997). Dreyfuss and Chapela (1994) estimated that endophytic fungi, alone could be ~1 million. The genetic diversity of fungal endophytes may be a major factor in the discovery of novel bioactive compounds (Gunatilaka, 2006). The true potential of these endophytes is yet to be tapped.

From the first reports of isolation from the Loliurn temulentum typically known as Darnel (ryegrass) by Freeman (1904), to the latest one from Antarctic moss (Melo et al., 2014), endophytic fungi have attracted the attention of botanists, chemists, ecologists, mycologists, plant pathologists and pharmacologists. It is estimated that each and every of the almost 300,000 plants that exist, hosts one or more endophyte (Strobel and Daisy, 2003). They occur everywhere, from the Arctic to Antarctic and temperate to the tropical climates. Endophytes reside in internal tissues of living plants but this association does not cause any immediate, overt, negative effects on the host plant (Bacon and White, 2000). According to Aly et al. (2011), the endophyte-plant host relationship is a balanced symbiotic continuum, ranging from mutualism through commensalism to parasitism. Many endophytic fungi remain quiescent within their hosts until it stressed or begins to undergo senescence. At this juncture the fungi may turn pathogenic (Rodriguez and Redman, 2008).

The impact of endophytes on our lives is seen in several of ways; from an insecticidal biofumigant from the Mucor musoabus, against adults and larvae of potato tuber moths (Lacey and Neven, 2006) to synthesis of “myco-diesel” by Gliocladium roseum, in the hope of alternate fuel options (Strobel et al., 2008). Between these extremes, endophytes has been shown to produce several pharmacologically important compounds such as antymycotics Cryptocin (Li et al., 2000) and Ambuic acid (Li et al., 2001), anticancer Torreyanic acid (Lee et al., 1995), Taxol (Strobel et al., 1996), anti-inflammatory Ergoflavin (Deshmukh et al., 2009), antidiabetic (nonpeptidal compound L-783,281) (Zhang et al., 1999), antioxidiant Pestacin (Harper et al., 2003), Isopestacin (Strobel et al., 2002), antiviral Cytocin acids A and B (Guo et al., 2000), alkaloids...
and polyketides Sclerotin A (Lai et al., 2013), Cryptosporioptide (Saleem et al., 2013), enzyme inhibitors- Fusaric acid derivatives (Chen et al., 2013), Antraquinones (Hawas et al., 2012) and immunosuppressive agents Subglutinols A and B (Lee et al., 1995).

The need for novel antibacterials to combat this increasing variety of infections becomes a priority endeavor. Endophytic fungi may be an important source for such biotherapeutics like new antibacterials against Mycobacterium tuberculosis especially in poverty ridden tropical countries of Asia. Here the need could also involve a nutritional efforts to boost the immunity in the population. Many of the compounds with their host plants are shown in Table 1.

**ANTIBACTERIALS FROM ENDOPHYTIC FUNGI COMPOUNDS FROM ASCOMYCETES**

Ascomycetes are an important class of fungi where there is formation of ascospores. Some genera of this class are prolific producer of bioactive metabolites. The genus Pestalotiopsis exists as an endophyte in most of the world’s rainforests and is extremely biochemically diverse. Some examples of products from this group are Ambuic acid (1) and its derivative (2) (Figure 1) isolated from a Pestalotiopsis sp. of the lichen Clavaroid sp. Compounds (1) and (2) are active against S. aureus (ATCC 6538) with IC₅₀ values of 43.9 and 27.8 μM, respectively (the positive control Ampicillin showed an IC₅₀ value of 1.40 μM) (Ding et al., 2009).

Pestalotiopen A (3) (Figure 1), from Pestalotiopsis sp. of the Chinese mangrove Rhizophora macrorhiza exhibited moderate antimicrobial activity against Enterococcus faecalis with an MIC value between 125 and 250 μg/mL (Hemberger et al., 2013).

A novel phenolic compound, 4-(2, 4, 7-trioxabicyclo[4.1.0]heptan-3-yl) phenol (4) (Figure 1) was isolated from Pestalotiopsis mangiferae associated with Mangifera indica. The compound exhibits activity against Bacillus subtilis and K. pneumoniae (MICs 0.039 μg/ml), E. coli and Micrococcus luteus (MICs 1.25 μg/ml) and P. aeruginosa (MIC 5.0 μg/ml). The positive control (Gentamycin) is showed activity against B. subtilis, K. pneumoniae and M. luteus, E. coli, and P. aeruginosa (MICs range 5.0–10.0 μg/ml). Transmission electron microscopy (TEM) analysis for mode of action of compound (4) showed that against the three human pathogens (E. coli, P. aeruginosa, and K. pneumoniae), morphological alterations took place: such as destruction of bacterial cells by cytoplasmic agglutination and formation of pores in cell wall membranes (Subban et al., 2013).

Pestalone (5) (Figure 1) is a chlorinated benzophenone antibiotic produced by a co-cultured Pestalotia sp./Uncinellar marine bacterium strain CNJ-328. Pestalotia sp. was isolated from the brown alga Rosenvingea sp. collected in the Bahamas Islands. Pestalone exhibits potent activity against MRSA (MIC 37 ng/mL) and VRE (MIC 78 ng/mL), indicating that Pestalone should be evaluated in advanced models of infectious disease (Cueto et al., 2001). It is active against S. aureus strain SG11, MRSA LT-1334 and Bacillus subtilis 168 with MICs of 3.1, 6.25, and 1.6 μg/mL respectively (Augner et al., 2013).

Phomopsis, another important genus exists as an endophyte in most plants and is also extremely biochemically diverse. Examples of bioactive metabolites from this endophyte are Dicerandrol A (6), B (7), and C (8) (Figure 1) from Phomopsis longicolla of the mint Dicerandra frutescens. They exhibit zones of inhibition of 11, 9.5, and 8.0 mm against B. subtilis respectively and 10.8, 9.5, and 7.0 mm respectively against S. aureus when tested at 300 μg/disc (Wagenaar and Clardy, 2001).

Dicerandrol C (8) (Figure 1) was isolated from Phomopsis longicolla strain C81, from the red seaweed Bostrychia radicans. Dicerandrol C (8) had significant antimicrobial activity against S. aureus (ATCC 6538) and Staphylococcus saprophyticus (ATCC 15305), with MICs of 1 and 2 μg/mL respectively (Erber et al., 2012). Dicerandrol C (8), Dicerandrol B (9), and Fusaric acid derivative (10) (Figure 1) were isolated from Phomopsis longicolla S1B4 from a plant sample from Hadong-gun, Kyungnam Province, South Korea. All of the above compounds show moderate to low antibacterial activities against Xanthomonas oryzae KACC 10331 with MICs of 8, 16, >16, 4, and 128 μg/mL respectively. Dicerandrol A (6) is also active against S. aureus KCTC 1916, B. subtilis KCTC 1021, Clavibacter michiganensis KACC 20122, Erwinia amylovora KACC 10060, with MICs value of 0.25, 0.125, 1.0, and 32.0 μg/mL respectively (Lim et al., 2010). Monodeacetylphomoxanthone B (11) (Figure 1) was reported from the same culture along with compounds (6–9). It is active against X. oryzae with an MIC of 32 μg/mL (Choi et al., 2013).

Phomoxanthone A (12) and B (13) (Figure 1) were obtained from Phomopsis sp. BCC 1323, of the leaf of Tectona grandis L., from the Mee Rim district of Chaingmai Province, Northern Thailand. These compounds show significant “in vitro” antibacterial activities with MICs of 0.5 and 6.25 μg/mL respectively against Mycobacterium tuberculosis H37Ra strain, in comparison to isoniazide and kanamycin sulfate (MICs of 0.050 and 2.5 μg/mL, respectively) that are used in clinics today (Isaka et al., 2001).

Phomoxanthone A (12) (Figure 1), was also isolated from a Phomopsis sp. of the stem of Costus sp. growing in the rain forest of Costa Rica. It has activity against Bacillus megaterium at a concentration of 10 mg/mL (radius of zone of inhibition of 3–4 cm) (Elsaesser et al., 2005).

Cycloexoylactone (14) (Figure 1) and cycloexoytriol B (15) (Figure 2) were detected from Phomopsis sp. (internal strain no. 7233) of Laurus azorica. They are moderately active against B. megaterium (Hussain et al., 2009a).

Phomosines A–C (16–18) (Figure 2), three new biaryl ethers were obtained from Phomopsis sp. of the leaves of Teucrium scorodonia. All three compounds were moderately active against B. megaterium and E. coli in vitro, using 6 mm filter paper disc with 50 μl each of a 15 mg/mL solution (Krohn et al., 1995). The same compounds were obtained from Phomosis sp. of Ligustrum vulgare and showed activity against B. megaterium in vitro with 10, 10, and 7 mm zone of inhibition using 6 mm filter paper disc and 50 μg of compound (50 μL of 1 mg/mL) respectively (Krohn et al., 2011).

Phomosine A (16) and Phomosine G (19) (Figure 2) were isolated from Phomopsis sp. of the halo tolerant plant Adenocarpus foliolosus from Gomera. Both the compound exhibited moderate antibacterial activity against Enterococcus faecalis with MICs of 1, 2, and 4 μg/mL respectively (Erber et al., 2012).
| Sr. No. | Fungus             | Plant source                    | Compounds isolated                      | Biological activity                                                                 | References                                      |
|--------|--------------------|---------------------------------|------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------|
| 1      | Pestalotiopsis sp. | Lichen Clavaroids sp            | Ambucic acid (1), Ambucic acid derivative (2) | Compound (1), *S. aureus* (ATCC 6538) (IC$_{50}$ 43.9 $\mu$M)                  | Ding et al., 2009                               |
|        |                    | Lichen Clavaroids sp            |                                          | Compound (2), *S. aureus* (ATCC 6538) (IC$_{50}$ 27.8 $\mu$M)                  | Ding et al., 2009                               |
| 2      | Pestalotiopsis sp. | *Rhizophora mucronata*          | Pestalotiospone A (3)                    | Compound (3), *E. faecalis* (MIC 125–250 $\mu$g/mL)                             | Hemberger et al., 2013                          |
| 3      | Pestalotiopsis mangiferae 1 | *Mangifera indica*           | 4-(2,4,7-trioxo-bicyclo[4.1.0]heptan-3-yl) phenol (4) | Compound (4), *B. subtilis* and *K. pneumoniae* (MIC 0.039 $\mu$g/mL), *E. coli* and *M. luteus* (MIC 1.25 $\mu$g/mL), *P. aeruginosa* (MIC 5.0 $\mu$g/mL). | Subban et al., 2013                             |
| 4      | Pestalotia sp. /Unicellular marine bacterium strain CNJ-328 | Co-cultured endophytic algal marine fungus/Unicellular marine bacterium strain CNJ-328 | Pestalone (5)                                          | Compound (5), MRSA (MIC 37 ng/mL), VRE (MIC 78 ng/mL)                         | Cueto et al., 2001                               |
| 5      | *Phomopsis longicolla* | *Dicerandra frutescens*         | Dicerandols A (6), B (7), and C (8)        | Compounds (6), (7) and (8), *B. subtilis* zones of inhibition of 11 mm, 9.5 mm and 8.0 mm respectively, *S. aureus* zones of inhibition of 10.8, 9.5 and 70 mm respectively at 300 $\mu$g/disk | Wagenaar and Clardy, 2001                        |
| 6      | *Phomopsis longicolla* strain CB1 | *Bostrychia radicans*         | Dicerandrol C (8)                                       | Compound (8), *S. aureus* (ATCC 6538) and *S. saprophyticus* (ATCC 15305), (MIC of 1 and 2 $\mu$g/mL) | Ebert et al., 2012                              |
| 7      | *Phomopsis longicolla* S1B4 | Unidentified plant             | Dicerandrol A (6), Dicerandrol B (7), Dicerandrol C (8), Deacetylphomoxanthone B (9), Fusaristatin A (10) | Compounds (6),(7), (8), (9) and (10), *X. oryzae* KACC 10331 (MIC of 8, 16, 32 and 64 $\mu$g/mL respectively), *X. oryzae* KACC 1916 (MIC of 16, 32, 64, 128 and 256 $\mu$g/mL respectively), *X. oryzae* KACC 10061 (MIC of 0.03125, 0.125, 0.25, 0.5, 1, 2, 4, 8, and 16 $\mu$g/mL respectively) | Lim et al., 2010                                 |
| 8      | *Phomopsis longicolla* S1B4 | Unidentified plant             | Dicerandrol A (6), Dicerandrol B (7), Dicerandrol C (8), Deacetylphomoxanthone B (9), and Monodeacetylphomoxanthone B (11) | Compound (11), *X. oryzae* (MIC of 32 $\mu$g/mL) | Choi et al., 2013                               |
| 9      | *Phomopsis* sp. BCC 1323 | Unidentified plant             | Phomoxanthone A (12) and B (13)                   | Compounds (12) and (13), *M. tuberculosis* H37Ra (MIC of 0.5 and 6.25 $\mu$g/mL respectively) | Isaka et al., 2001                              |
| 10     | *Phomopsis* sp.    | *Costus* sp.                    | Phomoxanthone A (12)                                    | Compound (12), *B. megaterium* (Zone of inhibition of 3-4 against the concentration of 10 mg/mL) | Elsaesser et al., 2005                           |

(Continued)
| Sr. No. | Fungus          | Plant source      | Compounds isolated                                                                 | Biological activity*                                                                 | References                  |
|---------|-----------------|-------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------|
| 11      | *Phomopsis* sp. | *Laurus azorica*  | Cycloepoxy lactone (14), Cycloepoxy triol B (15)                                    | Compounds (14) and (15), *B. megaterium* (moderate activity)                           | Hussain et al., 2009a       |
| 12      | *Phomopsis* sp. | *Teucrium scorodonia* | Phomosines A-C (16–18)                                                             | Compound (16–18), *B. megaterium* and *E. coli* (moderate activity in vitro using 6 mm filter paper disc with 50 μL of a 15 mg/mL solution) | Krohn et al., 1995         |
| 13      | *Phomopsis* sp. | *Ligustrum vulgare* | Phomosines A-C (16–18)                                                             | Compounds (16–18), *B. megaterium* (zone of inhibition with 10, 10 and 7 mm using 6 mm filter paper disc with 50 μg of compound). | Krohn et al., 2011         |
| 14      | *Phomopsis* sp. | *Adenocarpus foliolosus* | Phomosine A (16) and Phomosine G (19)                                               | Compounds (16) and (19), *B. megaterium* (moderate antibacterial activity)            | Dai et al., 2005           |
| 15      | *Phomopsis* sp. | *Notobasis syriaca* | Phomosine K (20), 2-hydroxymethyl-4β,5α,6β-trihydroxycyclohex-2-en (21), (−)-Phyllostine (22), (+)-Epiperoxid (23), and (−)-Epiperoxid monoacetate (24) | Compound (20), *Legionella pneumophila Corby, E. coli K12 and B. megaterium* (strong activity). Compound (21),(22),(23) and (24), *E. coli K12 and B. megaterium* (moderately active) | Hussain et al., 2011       |
| 16      | *Phomopsis* sp. | *Santolina chamaecyparissus* | Phomospinone B (25) and C (26)                                                      | Compounds (25) and (26), *E.coli, and B. megaterium* (moderately active)             | Hussain et al., 2012b      |
| 17      | *Phomopsis* sp. | Unidentified plant | Phomochromone A (27), B (28), Phomotenone (29), (1S,2S,4S)-trihydroxy-p-menthane (30) | Compounds (27-30), *E. coli and B. megaterium* (active)                                | Ahmed et al., 2011         |
| 18      | *Phomopsis* sp. | *Cistus salvifolius* | Pyrenocines J-M (31–34)                                                             | Compounds (31–34), *E. coli and B. megaterium* (active)                               | Hussain et al., 2012a      |
| 19      | Endophytic fungi | *Urobotrya siamensis*, *Grewia* sp., *Mesua ferrea*, *Rhododendron lyi*, *Tadehagi* sp., and *Gmelina elliptica* | 3-Nitropropionic acid (35)                                                          | Compound (35), *Mycobacterium tuberculosis* H37Ra (MIC of 3.3 μM)                     | Chomcheon et al., 2005     |
| 20      | *Phomopsis* sp. | *Erythrina crista-galli* | Phomol (36)                                                                         | Compound (36), *A. citreus* and *C. insidiosum* (MIC of 20 and 10 μg/mL respectively) | Weber et al., 2004         |
| 21      | *Phoma* sp.     | *Saurauia scaberinae* | Phomodione (37)                                                                    | Compound (37), *S. aureus* (MIC of 1.6 μg/mL)                                        | Hoffman et al., 2008       |
| 22      | *Phoma* sp.     | *Salsola oppositifolia* | Epoxydines B (38), Epoxydon (39), (4R,5R,6S)-6-acetoxy-4,5-dihydroxy-2-thydroxymethylcyclohex-2-one (40), 2-chloro-6-(hydroxymethyl) benzene-1,4-diol (41), antibiotic ES-242-1 (42) | Compounds (38–42), *E. coli and B. megaterium* (active)                                | Qin et al., 2010           |
Table 1 | Continued

| Sr. No. | Fungus | Plant source | Compounds isolated | Biological activity* | References |
|---------|--------|--------------|--------------------|----------------------|------------|
| 23      | Phoma sp. | Salsola oppositifolia | (+)-Flavipucine (43), (-)-Flavipucine (44) | Compound (43), B. subtilis, S. aureus, E. coli (zone of inhibition of 16, 17, and 11 mm, respectively in disc diffusion assay at 15 μg/6 mm disc), Compound (44), B. subtilis and E. coli (MICs of 25 μg/mL) | Loesgen et al., 2011 |
| 24      | Phoma sp. NRRL 46751, Saurauia scaberrinae |  | Phomapyrrolidone B (45), C (46) | Compound (45) and (46), M. tuberculosis H37Rv Microplate Alamar Blue assay (MABA) for replicating cultures (with MIC of 5.9 and 5.2 μg/mL respectively) Low oxygen recovery assay (LORA) (MIC 15.4 and 13.4 μg/mL respectively for nonreplicating) | Wijeratne et al., 2013 |
| 25      | Colletotrichum gloeosporioides | Artemisia mongolica | Colletotric acid (47) | Compound (47), B. subtilis, S. aureus, and S. lutea (MIC of 25, 50, and 50 μg/mL) | Zou et al., 2000 |
| 26      | Colletotrichum sp. Ilex canariensis |  | (22E,24R)-19(10->6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol (48), (22E,24R)-ergosta-4,7,22-trien-3-one (49), (22E,24R)-ergosta-4,6,8(14),22-tetraen-3-one (50), (22E,24R)-ergosta-7,22-dien-3β,5α,6β-triol (51), (22E,24R)-6-acetoxy-ergosta-7,22-dien-3β,5α,6β-triol (52), and (22E,24R)-3,6-diacetoxy-ergosta-7,22-dien-3β,5α,6β-triol (53) | Compounds (48–53), E. coli and B. megaterium active at the concentration of 0.05 μg/filter paper disc of 6 mm diameter | Zhang et al., 2009 |
| 27      | Coniothyrium sp. Sideritis chamaedryfolia |  | 1-hydroxy-5-methoxynaphthalene (54), 1,5-dimethoxy-4-nitronaphthalene (55), 1-hydroxy-5-methoxy-2,4-dinitronaphthalene (56) | Compounds (54–56), E. coli and B. megaterium (active) | Krohn et al., 2008a |
| 28      | Coniothyrium cereale | Marine green alga Enteromorpha sp. | (−)-Tryptophene (57) | Compound (57) Mycobacterium phlei, S. aureus, and E. coli, lat 20 μg/disk zones of inhibition of 18, 14, and 12 mm respectively | Elsebai et al., 2011 |
| 29      | Coniothyrium sp | Salsola oppositifolia | Pachybasin (58), 1,7-Dihydroxy-3-methyl-9,10-anthraquinone (59), Phomarin (60), 1-Hydroxy-3-hydroxymethyl-9,10-anthraquinone (61) and Coniothyrinones A-D (62–65) | Compounds (58–65), E. coli and B. megaterium (active at 50 μg/9 mm filter paper disc dissolved in acetone) | Sun et al., 2013a |
| 30      | Diaporthe phaseolorum | Laguncularia racemosa | 3-Hydroxypropionic acid (66) | Compound (66), S. aureus and S. typhi (MIC of 64 μg/mL) | Sebastianes et al., 2012 |
| Sr. No. | Fungus | Plant source | Compounds isolated | Biological activity* | References |
|--------|--------|--------------|--------------------|----------------------|------------|
| 31     | Botryosphaeria mamosae PSU-M76 | **Garcinia mangostana** | Botryomaman (67), 2,4-Dimethoxy-6-pentylphenol (68), trans-4-hydroxymellein (72), and 4,5-dihydroxy-2-hexenoic acid (73) | Compounds (67–73), S. aureus ATCC 25923 and MRSA SK1 (active), Compound (70) S. aureus ATCC 25923 and MRSA SK1 (MIC values of 8 μg/mL) | Pongcharoen et al., 2007 |
| 32     | Microdiplodia sp | Lycium intricatum | Diversonol (74), Microdiplodiasol (75), Microdiplodiasone (76), and Microdiplodiasolol (77) (−)-Gynuraone (78) and Ergosterol (79) | Compounds (74–79), Legionella pneumophila (active) | Siddiqi et al., 2011 |
| 33     | Microdiplodia sp. KS 75-1 | Pinus sp. | 7,8-dihydronivefuranone A (80), 7,8-dihydro-8-hydroxyterrefuranone (81), 6-hydroxyterrefuranone (82), Nivefuranones A (83) | Compounds (80–83), S. aureus NBRC 13276 (zone of inhibition of 15, 15, 16 and 15 mm respectively at 40 μg/per disc of 8 mm diameter) | Shiono et al., 2012 |
| 34     | Microsphaeropsis arundinis | Pinus sp. | 1β-hydroxy-α-cyperone (84) | Compound (84), S. aureus (CGMCC1.2465) (MIC 11.4 μg/mL) | Luo et al., 2013 |
| 35     | Microsphaeropsis sp. (strain 8875) | Lycium intricatum | Microsphaeropsone A (85), Microsphaeropsone C (86), Citreorosein (87) | Compounds (85–87), E.coli and B. megaterium (active) | Krohn et al., 2009 |
| 36     | Microsphaeropsis sp. (internal strain no. 7177) | Zygophyllum forteseii | Fusidenol A (88), aromatic xanthones (89), 3,4-dihydroxylobosuxanthone A (90) | Compounds (88–90), E.coli and B. megaterium (active) | Krohn et al., 2009 |
| 37     | Dinemasporium stigiosum | Calystegia sepium | Dinemasones A (91), B (92) | Compounds (91) and (92), B. megaterium (active) | Krohn et al., 2008b |
| 38     | Cytospora sp. CR200 and Diaporthe sp. CR146 | Conocarpus erecta and Forsteronia spicata | Cytosporones D (93), E (94) | Compound A (95), S. aureus ATCC 29923, S. aureus ATCC6538F, S. aureus #310 (MRSA), E. faecium #379 (VREF), E. faecium #436 (VSEF), B. subtilis BGGS1A1, E. coli imp BAS849, E. coli BAS849, E. coli ATCC25922, K. pneumoniae ATCC 10031, P. aeruginosa ATCC 27079 (MICs 0.03–0.25 μg/mL and compound (93) and (94), Above mentioned bacteria (MICs 8–64 μg/mL) | Brady et al., 2000 |
| 39     | Cytospora sp. CR200 | Conocarpus erecta | Cytosporones D (93), E (94) Cytoskyrin A (95) | Compound A (95), S. aureus ATCC 29923, S. aureus ATCC6538F, S. aureus #310 (MRSA), E. faecium #379 (VREF), E. faecium #436 (VSEF), B. subtilis BGGS1A1, E. coli imp BAS849, E. coli BAS849, E. coli ATCC25922, K. pneumoniae ATCC 10031, P. aeruginosa ATCC 27079 (MICs 0.03–0.25 μg/mL and compound (93) and (94), Above mentioned bacteria (MICs 8–64 μg/mL) | Singh et al., 2007 |
| Sr. No. | Fungus | Plant source | Compounds isolated | Biological activity* |
|--------|--------|--------------|--------------------|---------------------|
| 40     | Cytospora sp. | Ilex canariensis | (R)-5-((S)-hydroxy(phenyl)-methyl)dihydrofuran-2(3H)-one (96) and its 6-acetate (97), a new naphthalenone derivative (98), (S)-5-((S)-hydroxy(phenyl)-methyl)dihydrofuran-2(3H)-one (99), (S)-5-benzyl-dihydrofuran-2(3H)-one (100), 5-phenyl-4-oxopentanoic acid (101), gamma-oxo-benzenepentanoic acid methyl ester (102), 3-(2,5-dihydro-4-hydroxy-5-oxo-3-phenyl-2-furyl)propionic acid (103), (3R)-5-methylmellein (104), Integracins A (105) and B (106) | Compounds (96–106), B. megaterium (zone size in the range of 15–25 mm when 50 μl of the solution (0.05 mg substance) were pipetted onto a sterile filter disc) |
| 41     | Chaetomium globosum Viguiera robusta | | Chaetoglobosin B (107) | Compound (107), S. aureus (MIC 120 μg/mL) and E. coli (MIC 180 μg/mL) |
| 42     | Chaetomium globosum strain IFB-E036 | Cynodon dactylon | Chaetoglobocins A (108), B (109) | Compounds (108) and (109), B. subtilis, S. pyogens, M. luteus and M. smegmatis (MIC between 8 and 32 μg/mL) |
| 43     | Chaetomium globosum SNB-GTC2114 | Paspalum virgatum | Acremonisol A (110), Semicochliodinol A (111), Cochliodinol (112) | Compounds (110) and (111), S. aureus ATCC 29213 (MIC of 64, 2 and 4 μg/mL respectively) |
| 44     | Lewia infectoria SNB-GTC2402 | Besleria insolita | Pyrrocidine A (113), Pyrrocidine B (114) | Compounds (113–114), S. aureus ATCC 29213, (MIC value of 5 μg/mL) |
| 45     | Xylaria sp. | Ginkgo biloba | 7-amino-4-methylcoumarin (117) | Compounds (117), S. aureus, E. coli, S. typhi, S. typhimurium, S. enteritidis, A. hydrophila, Yersinia sp., V. anguillarum, Shigella sp., and V. parahaemolyticus (MIC of 16, 10, 20, 15, 8.5, 4, 12.5, 25, 6.3, and 12.5 μg/mL respectively) |
| 46     | Xylaria sp. | Torreya jackii | 1-(xylarenone A) xylariate A (118), Xylarioic acid B (119), Xylarioic acid A (120), Xylarioic acid B (121), Xylarioide C (122), Xylarioide D (124), Tawagryme C (125) | Compounds (118–125), E. coli ATCC 2922, B. subtilis ATCC 9372, and S. aureus ATCC 25923 (MIC values above 10 μg/mL) |
| 47     | Cryptosporiopsis sp. | Viburnum tinus | Cryptosporioptide (126) | Compound (126), B. megaterium (with a 9 mm radius of the zone of inhibition) |
| Sr. No. | Fungus                      | Plant source     | Biological activity                           | References                        |
|--------|-----------------------------|------------------|-----------------------------------------------|-----------------------------------|
| 48     | Microdochium bolleyi        | Fagonia cretica  | Compounds (127–129); E. coli and B. megaterium (active) | Zhang et al., 2008a               |
|        |                             |                  | Compounds (130) and (131); 8-subs; with zone of inhibition 23 and 22 mm, respectively (15 μg/6-mm filter disks). Compound (130), S. aureus and E. coli (with zone of inhibition 9 and 8 mm, respectively (15 μg/6-mm filter disks). Compounds (132) and (133); 8-subs; with zone of inhibition of 16.4 ± 0.3 mm at 3 μg/disk | Loesgen et al., 2008              |
| 49     | Chalara sp. strain 6661     | Artemisia vulgaris| Isofusidienol A, B, C, and D (130–133) | Compounds (130) and (131) | B. subtilis (with zone of inhibition 23 and 22 mm, respectively (15 μg/6-mm filter disks). Compound (130), S. aureus and E. coli (with zone of inhibition 9 and 8 mm, respectively (15 μg/6-mm filter disks). Compounds (132) and (133); 8-subs; with zone of inhibition of 16.4 ± 0.3 mm at 3 μg/disk | Loesgen et al., 2008              |
| 50     | Blennoria sp.               | Carpobrotus edulis| Secalonic acid B (134) | Blennolides A (135), and B (136) | Compounds (134–136), B. megaterium (active). Compounds (135) and (136), E. coli (active) | Zhang et al., 2008b               |
| 51     | Preussia sp.                | Aquilaria sinensis| Spiropreussione A (137) | Compound (137), S. aureus (CMCC B26003) | Zone of inhibition of 16.4 ± 0.3 mm at 3 μg/disk, MIC 25 μg/mL | Chen et al., 2009                  |
| 52     | Guignardia sp. IFB-E028     | Hopea hainanensis| Monomethylsulochrin (138), Rhizoctonic acid (139), Guignasulfide (140) | Compound (138–140), R. solanacearum and S. aureus and X. vesicatoria (MICs 1.56, 3.13, and 1.56, respectively) | MIC values of 28.9, 60.2, and 42.9 μM, respectively. Compounds (145–149), M. tuberculosis strain H37Rv. (MICs 12.5, 25.0, 42.1, 48.2, and 50.0 μg/mL) | Wang et al., 2010                  |
| 53     | Pichia guilliermondii       | Paris polyphylla var. yunnanensis | Helvolic acid (141) | A. tumefaciens, E. coli, P. lachrymans, R. solanacearum, X. vesicatoria, B. subtilis, S. aureus and S. haemolyticus, (MICs 1.56, 3.13, 3.13, 1.56, 1.56, 3.13, 50, and 6.25 μg/mL) | Compound (141), S. aureus ATCC 25923 and MRSA ATCC 33591 (MICs 128 and 256 μg/mL respectively) | Zhao et al., 2010                  |
| 54     | Dothideomycete sp.          | Tiliacora triandra | Chlorogenic acid (142) | (Antibacterial, antifungal, antioxidant, and antitumor activities) | Compound (142), S. aureus ATCC 25923 and MRSA ATCC 33591 (MICs 128 and 256 μg/mL respectively) | Senadeera et al., 2012 |
| 55     | Eurotium cristatum EN-220   | Sargassum thunbergii | Cristatumins A (151), Tardioxopiperazine A (152) | Compounds (151) and (152), E. coli and S. aureus IMCs 64 | MICs 12.5, 25.0, 42.1, 48.2, and 50.0 μg/mL | Du et al., 2005                  |
| 56     | Aspergillus sp. CY725       | Cynodon dactylon | Helvolic acid (141), Monomethylsulochrin (138), Ergosterol (79), 3β-hydroxy-4,5-epoxyergosta-4,7-dien-3-one (138) | Compound (141), S. aureus ATCC 25923 and MRSA ATCC 33591 (MICs 128 and 256 μg/mL respectively) | Compound (141), S. aureus IMCs 64 | 20.0 μg/mL respectively | Du et al., 2005                  |
| Sr. No. | Fungus | Plant source | Compounds isolated | Biological activity* | References |
|---------|--------|--------------|---------------------|----------------------|------------|
| 59      | Aspergillus sp. | Mixed cultured mycelia of two marine-derived mangrove epiphytic fungi | Aspergicin (154), Neoaspergillic acid (155) | 
|         |        |              |                     | 
|         |        |              |                     | 
|         |        |              |                     | Zhu et al., 2011 |
| 60      | Aspergillus sp. | Brown alga *Bruguiera gymnorrhiza* | Aspergillumarin A (156), B (157) | 
|         |        |              |                     | 
|         |        |              |                     | Li et al., 2012 |
| 61      | Aspergillus versicolor | Brown alga *Sargassum thunbergii* | Brevianamide M (158), 6,8-di-O-methylaverufin (159), 6-O-methylaverufin (160) | 
|         |        |              |                     | Miao et al., 2012 |
| 62      | Aspergillus versicolor | Red Sea green alga *Halimeda opuntia* | Isorhodoptilometrin-1-Me ether (161), Siderin (162) | 
|         |        |              |                     | Hawase et al., 2012 |
| 63      | Aspergillus wentii | *Gymnogongrus flabelliformis* pt-1 | Yicathin B (163), Yicathin C (164) | 
|         |        |              |                     | Sun et al., 2013b |
| 64      | Aspergillus sp. | *Bauhinia guianensis* EJC08 | Fumigaclavine C (165), Pseurotin A (166) | 
|         |        |              |                     | Pinheiro et al., 2013 |
| 65      | Penicillium sclerotiorum | *PSU-A13.* (+)-Sclerotiorin (167) | Compound (167), *S. aureus* sub sp. *aureus* ATCC 29213, (MIC 128 μg/mL) | 
|         |        |              |                     | Lucas et al., 2007; Arunpanichlert et al., 2010 |
| 66      | Penicillium janczewskii | *Prumnopitys analina* | Pseurotin A (166) | 
|         |        |              |                     | Schmeda-Hirschmann et al., 2010 |
| 67      | Penicillium citrinum | *Bruguiera gymnorrhiza* | Emodin (168), Erythritol (169) | 
|         |        |              |                     | Li et al., 2010 |
| 68      | Penicillium chrysogenum | *Laurencia*sp | Conidiogenone B (170), Conidiogenone (171) | 
|         |        |              |                     | Gao et al., 2011 |
| 69      | Penicillium chrysogenum | *Porteresia coarctata* | 3′,1′-di-dehydro-3′,2′-di-O-methylprotopiperazine-3′,2′,5-dione (172) | 
|         |        |              |                     | Devi et al., 2012 |
| Sr. No. | Fungus | Plant source | Compounds isolated | Biological activity |
|--------|--------|--------------|--------------------|---------------------|
| 70     | Penicillium citrinum | Ocimum tenuiflorum | Perinadine A | antibiotic activity |
| 71     | Fusarium sp. YG-45 | Maackia chinensis | Fusapyridon A | antibiotic activity |
| 72     | Fusarium oxysporum | Cinnamomum kanehirae | Beauvercin | antibiotic activity |
| 73     | Fusarium sp. BCC14842 | Bamboo | Javanicin, 3-O-methylfusarubin | antibiotic activity |
| 74     | Fusarium sp. | Ficus carica | Fumitremorgin B, C, Helvolic acid, Bisdethiobis(methylthio) gliotoxin, Bis-N-norgliovietin, Gliotoxin | antibiotic activity |
| 75     | Fusarium sp. | Artocarpus paunchenys | Lateropyrone | antibiotic activity |
| 76     | Fusarium sp. | Astrocaryum Bambuceae | Fusarium sp. | antibiotic activity |

References:

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23. C. L. H. de Melo et al., 2011
| Sr. No. | Fungus          | Plant source                        | Compounds isolated                    | Biological activity*                                      | References     |
|--------|-----------------|-------------------------------------|---------------------------------------|-----------------------------------------------------------|----------------|
| 79     | *Fusarium solani* | *Rheum palmatum* L.                | Rhein *(195)*                         | Compound *(195)*, *S. aureus*, *S. aureus* nor A, *B. megaterium* 11561, *P. syringae* and *S. melliloti* (MICs in the range of 0.6–4 μg/mL) | *You et al., 2013* |
| 80     | *Fusarium proliferatum* BLHS51 | *Macleaya cordata*                | Sanguinarine *(196)*            | Sanguinarine *(196)*, 15 clinical isolates of *S. aureus* (MIC range of 3.12–6.25 μg/mL) Two reference strains ATCC 292. (MIC are 3.12 μg/mL), ATCC 33591 (MIC 1.5 μg/mL) | *Wang et al., 2014* |
| 81     | *Trichoderma ovalisporum* strain PRE-5 | *Panax notoginseng*            | Shikimic acid *(197)*              | Compound *(197)*, *S. aureus*, *Bacillus cereus*, *M. luteus* and *E. coli* (Active) | *Dang et al., 2010* |
| 82     | *Trichoderma* sp. PR-35 | *Paeonia delavayi*               | Trichoderic acid *(198)*, 2β-hydroxytrichoacorenol *(199)*, Cyclonerylod *(200)*, Cycloneryl oxid *(201)*, and Sorbicillin *(202)* | Compounds *(198–202)*, *E. coli* and *S. albus* (MIA values in the range of 25–150 μg/disk). Compounds *(198)*, *(200)*, and *(201)*, *S. sonnei* (MIA values in the range of 100–150 μg/disk) | *Wu et al., 2011* |
| 83     | *Trichoderma asperellum* | *Panax notoginseng*            | PF1022F *(203)*, Halobacillin *(204)* | Compounds *(203)* and *(204)*, *E. faecium* (IC50 7.30 and 5.24 μM respectively), *S. aureus* COL (IC50 19.02 and 14.00 μM respectively) | *Ding et al., 2012* |
| 84     | *Nigrospora* sp. MA75 | *Pongamia pinnata*               | Tetrahydrobostrycin *(205)*, 4-deoxytetrahydrobostrycin *(206)*, 3,6,8-trihydroxy-1-methylxanthone *(207)*, Griseophenone C *(208)* and 2,3-didehydro-19α-hydroxy-14-epicochloiquinone B *(209)* | Compound *(209)*, MRSA, *E. coli*, *Paeurginosa*, *P. fluorescens*, and *S. epidermidis* (MICs 8, 4, 4, 0.5, and 0.5 μg/mL, respectively). Compound *(208)*, MRSA, *E. coli*, *P. aeruginosa*, and *P. fluorescens* (MICs 0.5, 2, 0.5, and 0.5 μg/mL respectively). Compound *(205)*, MRSA and *E. coli* (MIC 2 and 0.5 μg/mL, respectively), Compound *(206)*, *E. coli* (MIC 5 μg/mL) Compound *(207)*, *S. epidermidis* (MIC 0.5 μg/mL) | *Shang et al., 2012* |
| 85     | *Nigrospora* sp | Plant collected from South China Sea | 4-deoxybostrycin *(210)*, Nigrosporin *(211)* | Compounds *(210)* and *(211)*, *M. tuberculosis* and clinical multidrug-resistant (MDR) *M. tuberculosis* strains (MICs <5 μg/mL) | *Wang et al., 2013b* |
| 86     | *Periconia* sp. | *Taxus cuspidata*                | Periconicins A *(212)* and B *(213)* | Compounds *(212)*, *B. subtilis*, *S. aureus*, *K. pneumoniae*, and *Salmonella typhi* (MICs in the range of 3.12–12.5 μg/mL) | *Kim et al., 2004* |
| 87     | *Periconia* sp. | *Piper longum*                  | Piperine *(214)*                    | Compound *(214)*, *M. tuberculosis* and *M. smegmatis* (MIC of 1.74 and 2.62 μg/mL respectively) | *Verma et al., 2011* |

(Continued)
| Sr. No. | Fungus | Plant source | Compounds isolated | Biological activity* | References |
|--------|--------|--------------|--------------------|----------------------|------------|
| 88     | *Periconia siamensis* CMUGE015 | Thysanoleana latifolia | Modiolide A, 6,8-dihydroxy-10-methy-5, 8, 9, 10-tetrahydro-2H-oxacin-2-one (215), 4-Chromanone, 6-hydroxy-2-methyl-15(3CI) (216) | Compound (215), *B. cereus*, *L. monocytogenes*, MRSA, *P. aeruginosa* and *E. coli* (MIC of 3.12, 6.25, 25.00, 12.50 and 50.00 μg/mL respectively). Compound (216), *B. cereus*, *L. monocytogenes*, MRSA, *P. aeruginosa* and *E. coli* (MIC of 6.25, 12.50, 25.00, 12.50 and 100.00 μg/mL respectively) | Bhilabutra et al., 2007 |
| 89     | *Alternaria* sp. | Sonneratia alba | Xanalteric acids I and II (217, 218), Altenusin (219) | Xanalteric acids I and II (217, 218), Multidrug-resistant *S. aureus* (MIC 250–125 μg/mL respectively). Altenusin (219), MRSA, *S. pneumonia*, *E. faecium*, *E. cloacae* and *A. faecalis* (MIC values of 31.25–125 μg/mL) | Kjer et al., 2009 |
| 90     | *Nodulisporium* sp. | Juniperus cedre | 1-(2,6-dihydroxyphenyl)butan-1-one (220) | Compound (220), *B. megaterium* (zone of inhibition 15 mm at a concentration of 0.25 mg/filter disc) | Dai et al., 2006 |
| 91     | *Nodulisporium* sp. | Erica arborea | Nodulisporins D-F (221–223), benzene-1,2,3-triol (224) | Compounds (221–224), *B. megaterium* (Active) Dai et al., 2009b |
| 92     | *Acremonium zeae* | Maize plant | Pyrocidine A (113) | Compound (113), *C. michiganense* subspp. *nebraskense*, *B. megaterium* (MIC 1–2 μg/mL) and *P. fluorescens* (MIC 1–2 μg/mL) | Wicklow and Pilling, 2009 |
| 93     | *Rhizoctonia* sp. (Cy064), *Cynodon dactylon* | | Rhizoctonic acid (139), Monomethylsulochrin (138), Ergosterol (79), 3β,5α,6β-trihydroxyergosta-7,22-diene (225) | Compounds (139, 138, 79, 225), five clinical and one reference isolate of *H. pylori* (ATCC 43504) (MICs in the range of 10.0–30.0 μg/mL) | Ma et al., 2004 |
| 94     | *Ulocladium* sp. | Lichens | Ophiobolins P (226), T (227) | Ophiobolins P (226), *B. subtilis* and MRSA (MIC of 62.5 and 31.3 μg/mL respectively). Ophiobolin T (227), *B. subtilis* and MRSA. *S. aureus* and Bacille Calmette-Guerin strain (MIC of 31.3 μg/mL respectively) | Wang et al., 2013a |
| 95     | *Chloridium* sp | Azadirachta indica | Javanicin (181) | Javanicin (181), *P. fluorescens* and *P. aeruginosa* (MIC of 2 μg/mL) | Khrawar et al., 2009 |
| 96     | *Botryosphaeria rhodina* PSU-M35 and PSU-M114 | *Garcinia mangostana* | *β*3-lasiodiplodin (228), *IR*–*−*–mellein (229), cis-*IR*,4R,*IR*–*−*–4-hydroxymellein (230), trans-*IR*,4R,*IR*–*−*–4-hydroxymellein (231), *IR*–*−*–1-hydroxymellein (232) | Compound (228), *S. aureus* and MRSA (MICs 64 and 128 μg/mL respectively). Compounds (229–232), *S. aureus* and MRSA (MIC value of >128 μg/mL) | Rukachaisirikul et al., 2009 |
| 97     | *Fusidium* sp. | leaves of Mentha arvensis | Fusidilactones D (233), E (234) | Compounds (233–234), *E. coli* and *B. megaterium* (active) | Qin et al., 2009 |

(Continued)
Table 1 | Continued

| Sr. No | Fungus | Plant source | Compounds isolated | Biological activity* | References |
|-------|--------|--------------|--------------------|----------------------|------------|
| 98    | Hyalodendriella sp | hybrid "Neva" of *Populus deltoides* Marsh × *P. nigra* L. | Palmariol B (235), 4-hydroxymellein (236), alternarial 9-methyl ether (237), Botrallin (238) | Compounds (235–238), *A. tumefaciens* (IC50 values ranged from 18.22 µg/mL to 87.52 µg/mL), *B. subtilis*, *P. lachrymans*, *R. solanacearum*, *X. vesicatoria*, *E. coli*, *A. tumefaciens*, *X. vesicatoria*, *P. lachrymans* and *B. subtilis* (MIC ranges from 50 to 100 µg/mL) | Meng et al., 2012 |
| 99    | Stemphylium globuliferum | *Mentha pulegium* (Lamiaceae) | Alterporriol N (239), alterporriol D (240), alterporriol E (241) | Compound (239), MRSA and *E. faecalis* (MIC of 62.5 and 15.63 µg/mL), Compound (240), MRSA and *S. pneumonia* (MIC of 31.25 µg/mL each), Compound (241), *S. pneumonia*, *E. faecalis* and *E. cloacae* (MIC of 31.25 µg/mL each) | Debbab et al., 2009 |
| 100   | Endophytic fungus, no. 1403 | Mangrove | Bostrycin (242) | Bostrycin (242), *B. subtilis* (Active) | Charudattan and Rao, 1982; Xu et al., 2010a |
| 101   | Costa Rican fungus CR115 | *Daphnopsis americana* | Guanacastepene A (243) | Guanacastepene A (243), MRSA and VRE (Active) | Singh et al., 2000 |
| 102   | Costa Rican fungus CR115 | *Daphnopsis americana* | Guanacastepene I (244) | Guanacastepene I (244), *S. aureus* (Active in agar diffusion assay) | Brady et al., 2001 |
| 103   | Endophytic fungus No. B77 | Mangrove tree | Anhydrofusarubin (245) | Compound (245), *S. aureus* (ATCC 27154) (MIC 12.5 µg/mL) | Shao et al., 2008b |
| 104   | Endophytic fungus B77 | seed of the mangrove sample *Kandelia candel* | 3-O-methylfusarubin (182), fusarubin (246) | Compounds (182) and (246), *S. aureus* ATCC 27154 (MIC value of 50.0 and 12.5 µg/mL, respectively) | Shao et al., 2008a |
| 105   | Endophytic fungus PSU-N24 | *Garcinia nigrolineata* | Compound 2 (247), 9a-hydroxylorosellinia A (248) and desoxybostrycin (249) | Compound (248), *M. tuberculosis* (MIC 12.50 µg/mL), Compounds (247) and (249), (MIC 25 and 50 µg/mL, respectively) | Sommart et al., 2008 |
| 106   | Endophytic fungus S20 | *Cephalotaxus hainanensis* Li. | Indolyl-3-carboxylic acid (250) | Compound (250), *S. aureus* and MRSA (Zones of inhibition 12 and 8 mm, respectively when 50 µl (10 mg/mL) of the compound was impregnated on sterile filter paper discs (6 mm diameter) | Dai et al., 2009a |
| 107   | Endophytic fungus S20 | *Cephalotaxus hainanensis*. | 5-acyl-2-methylpyrrole (251) | Compound (251), *S. aureus* MRSA (Zone of inhibition of 12.0 mm and 10.0 mm respectively when 50 µl (10 mg/mL) of the compound was impregnated on sterile filter paper discs (6 mm diameter) | Dai et al., 2009c |
| 108   | Endophytic fungus Dzf12 | *Dioscorea zingiberensis* | Diepoxin α (252), Diepoxin η (253), Diepoxin ζ (254) | Compound (252), *E. coli*, *A. tumefaciens*, *X. vesicatoria*, *P. lachrymans* and *B. subtilis* (MIC ranges from 50 to 100 µg/mL). The mixture of Compounds (253) and (254), *E. coli*, *A. tumefaciens*, *X. vesicatoria*, *P. lachrymans* and *B. subtilis* (MIC ranges from 5.0 to 12.5 µg/mL) | Cai et al., 2009 |
Table 1 | Continued

| Sr. No. | Fungus | Plant source | Biological activity | Compounds isolated | References |
|---------|--------|--------------|---------------------|--------------------|----------------|
| 109     | An unidentified ascomycete from Melilotus dentatus | E. coli (Active) and B. megaterium (Active) | Compounds (255) and (256), E. coli compounds (256) | Guignardone I (263), S. aureus | Hussain et al., 2011 |
| 110     | Unidentified ascomycete from Arbutus unedo | Pestalotheols E-H (258–261) | Compounds (258–262), E. coli and B. megaterium (Active) | Guignardone B (264), MRSA | Qin et al., 2011, Ymele-Leki et al., 2012 |
| 111     | Endophytic fungus A1 from Guignardone I and Guignardone B (263) | | | | |
|         |                                   |                          | Guignardone I (263), S. aureus (MIC of 9.0 and 11.0 mm in diameter at 65 M, respectively (the diameter of sterile filter paper discs was 6 mm). Guignardone B (264), MRSA | | |
|         |                                   |                          |                     | Ymele-Leki et al., 2012 |
| 112     | Endophytic fungus A1 from Neomirandea angularis | Mirandamycin (265), E. coli Z5922, P. aeruginosa Z5857, K. pneumoniae carbapenemase positive BAA-1705, MRSA, BAA-976 and PW357 (MIC of 80, 80, > 80 and 10 μg/mL respectively) | Mirandamycin (265) | | |

*Data as reported by authors.

Antibacterials from endophytic fungi

Phomosine K (20), 2-hydroxymethyl-4β,5α, 6β-trihydroxycyclohex-2-en (21), (-)-Phyllostine (22), (+)-Epiploxydon (23), and (+)-Epiploxydon monoacetate (24) (Figure 2) were isolated from a Phomopsis sp. of Notobasis syriaca. Phomosine K (20) is active against Legionella pneumophila Corby, E. coli K12 and B. megaterium in vitro while 2-hydroxymethyl-4β,5α,6β-trihydroxycyclohex-2-en (21), (-)-Phyllostine (22), (+)-Epiploxydon (23), and (+)-Epiploxydon monoacetate (24) showed moderate activities against E. coli K12 and B. megaterium (Hussain et al., 2011).

Phomospinone B (25) and C (26) from a Phomopsis sp. present in stems of Santolina chamaecyparissus from Sardinia showed moderate activities against E. coli, and B. megaterium (Hussain et al., 2012b).

Phomochromone A (27), B (28), Phomotenone (29), and (1S, 2S, 4S)-trihydroxy-p-methane (30) (Figure 2) were isolated from a Phomopsis sp. of Cistus monspeliensis. All three compounds (27–30) show activity against E. coli and B. megaterium (Ahmed et al., 2011).

Pyrenocines J-M (31–34) (Figure 2) were isolated from a Phomopsis sp. of the plant Cistus salviifolius, internal strain 7852. All four compounds (31–34) are active against B. megaterium and E. coli (Hussain et al., 2012a).

3-Nitropropionic acid (35) (Figure 2) was isolated from several strains of endophytic fungus of the genus Phomopsis sp. obtained from six species of Thai medicinal plants (Table 1) from the forest areas of Chiangmai, Nakhonratchasima, and Pitsanulok Provinces of Thailand. 3-Nitropropionic acid exhibits potent activity against Mycobacterium tuberculosis H37Ra with the MIC of 3.3 μM, but no in vitro cytotoxicity was observed toward a number of cell lines (Chomcheon et al., 2005). 3-Nitropropionic acid is known to inhibit isocitrate lyase (ICL), an enzyme required for fatty acid catabolism and virulence in M. tuberculosis (Muñoz-Elias and McKinney, 2005).

Phoma is another genus which produces diverse compounds. Here are some examples of bioactive compounds produced by this genus. Phomol (36) (Figure 3), a novel antibiotic, was isolated from a Phomopsis sp. of the medicinal plant Erythrina cristagalli. Phomol is active against Arthrobacter citreus and Corynebacterium insidiosum with MICs of 20 and 10 μg/mL respectively (Weber et al., 2004).

Phomodione (37), an usnic acid derivative was isolated from a Phoma sp. of Sauraria scaberrima. Phomodione was found to be effective against S. aureus at a MIC of 1.6 μg/mL (Hoffman et al., 2008).

The antibacterials Epoxycycle B (38), Epoxycycle A (39), (4R, 5R, 6S)-6-acetoxy-4,5-dihydroxy-2-(hydroxymethyl)cyclohex-2-en-1-one (40), 2-chloro-6-(hydroxymethyl)benzene-1,4-diol (41), and the antibiotic ES-242-1 (42) (Figure 3), were isolated from a Phoma sp. of Salsola oppositifolia. Compounds (38–42) show activity against E. coli and B. megaterium (Qin et al., 2010).

Antibacterials (+)-Flavipucine (43) and (-)-Flavipucine (44) (Figure 3), were isolated from a Phoma sp., of the plant Salsola oppositifolia. (+)-Flavipucine (43) is active against B. subtilis,
S. aureus, E. coli with inhibition zones of 16, 17, and 11 mm, respectively in disc diffusion assay at 15 μg/6 mm. (−)-Flavipucine (44) was active against B. subtilis and E. coli at MIC of 23 μg/mL (Loesgen et al., 2011).

Three new alkaloids, Phomapyrrolidones B-C (45–46) (Figure 3), were isolated from a Phoma sp. NRRL 46751, of the plant Saurauia scaberrinae. Phomapyrrolidones B (45) and C (46) show weak in vitro activities when tested in microplate Alamar
FIGURE 2 | Structures of antibacterial metabolites isolated from Ascomycetes (15–35).

- Cycloepoxytril B (15)
- R= CHO Phomosine A (16)
- R= MePhomosine K (20)
- Phomosine B (17)
- Phomosine C (18)
- Phomosine G (19)
- 2-hydroxymethyl-4β,5α, 6β-trihydroxy-cyclohex-2-en (21)
- (-)-Phyllistine (22)
- R=H (+)-Epiepoxydon (23)
- R=Ac (+)-Epoxydon monoacetate (24)
- R=H, R1=β-OH Phomopsinone B (25)
- R=H, R1=α-OH Phomopsinone C (26)
- Phomochromone A (27)
- Phomochromone B (28)
- Phomitenone (29)
- (1S,2S,4S)-trihydroxy-p-menthane (30)
- R1=R2=H Pyrenocine J (31)
- R1=*=O*(keto), R2=CH3 Pyrenocine K (32)
- R=OAc Pyrenocine L (33)
- R=H Pyrenocine M (34)
- 3-Nitropropionic acid (35)
FIGURE 3 | Structures of antibacterial metabolites isolated from Ascomycetes (36–47).
Blue assays (MABA) with MICs of 5.9 and 5.2 μg/mL respectively and in the low oxygen recovery assay (LORA) with MICs of 15.4 and 13.4 μg/mL respectively, for nonreplicating \textit{M. tuberculosis} H37Pv (Wijeratne et al., 2013).

Other endophytes of Ascomycetes are also known to produce antibacterials. For example Colletotric acid (47) (Figure 4) from \textit{Colletotrichum gloeosporioides} of Artemisia mongolica or Nanjing, China inhibits \textit{B. subtilis}, \textit{S. aureus}, and \textit{Sarcina lutea} with MICs of 25, 50, and 50 μg/mL, respectively (Zou et al., 2000).

Antibacterials (22E,24R)-19(10>6)-abeo-ergosta-5,7,9,22-tetraen-3β-ol (48), (22E,24R)-ergosta-4,7,22-trien-3-one (49), (22E,24R)-ergosta-4,6,8(14),22-tetraen-3-one (50), (22E,24R)-ergosta-7,22-dien-3β,5α,6β-triol (51), (22E,24R)-6-acetoxy-ergosta-7,22-dien-3β,5α,6β-triol (52), and (22E,24R)-3,6-diacetoxy-ergosta-7,22-dien-3β,5α,6β-triol (53) (Figure 4), were isolated from a \textit{Colletotrichum} sp. of \textit{Ilex canariensis} from Gomera. Compounds (48–53) are active against \textit{E. coli} and \textit{B. megaterium} of 0.05 μg/fil filter paper disc of 6 mm

![Figure 4](https://example.com/image.png)

**FIGURE 4** | Structures of antibacterial metabolites isolated from Ascomycetes (48–64).
biogenetic Anthraquinoid and Citreorosein (87). From a Microsphaeropsis species (strain no. 7177) of the plant Zygothyllum fortanessii from Gomera (Spain), large amounts of Fusidienol A (88) and the known aromatic xanthones (89), were isolated. The endophyte Seimatosporium species (internal strain no. 8883) of Salsola oppositifolia from Gomera (Spain), produced 3, 4-dihydroglobsuxanthone A (90). Compounds (85–90) were active against E. coli and B. megaterium (Krohn et al., 2009).

Dinemasones A(91) and B (92) (Figure 5), were isolated from Dinemasporum strigosum obtained from the roots of the herbaceous plant Calystegia sepium growing on the shores of the Baltic Sea, Wustrow, Germany. The above compounds showed antibacterial activities against B. megaterium (Krohn et al., 2008b).

Cytosporone D (93) and E (94) (Figure 7), were isolated from the endophyte CR200 (Cytospora sp.) and CR146 (Diaportha sp.) present in tissues of Conocarpus erecta and Forsteronia spicata plants respectively collected in the Guanacaste Conservation Area of Costa Rica. Cytosporone D (93) shows antibacterial activity against S. aureus, E. faecalis, and E. coli with MICs of 8, 8, and 64 μg/mL respectively, while Cytosporones E (94) has similar activity against S. aureus (Brady et al., 2000).

Cytosporone D (93), E (94), and Cytoskynin A (95) (Figure 7), were isolated from a Cytospora sp. CR200 from a branch of Conocarpus erecta (Buttonwood tree) in the Guanacaste National Park, from Costa Rica. Cytoskynin A (95) has good in-vitro antibacterial activity (MICs against (S. aureus ATCC 29923, S. aureus ATCC6538P, S. aureus #310 (MRSA), E. faecium #379 (VREF), E. faecium #436 (VSEF), B. subtilis BGGSA1, E. coli imp BAS849), ranging from 0.03 to 0.25 μg/mL). Cytosporone D (93) and E (94) have moderate in-vitro antibacterial activity against above mentioned bacteria (MICs 8–64 μg/mL) (Singh et al., 2007).

Two new benzyl γ-butyrolactone analogs, (R)-5-((S)-hydroxy(phenyl)-methyl)dihydrofuran-2(3H)-one (96) and its 6-acetate (97), a new naphthalenone derivative (98), together with aromatic derivatives, (S)-5-((S)-hydroxy(phenyl)-methyl) dihydrofuran-2(3H)-one (99), (S)-5-benzyl-dihydrofuran-2(3H)-one (100), 5-phenyl-4-oxopanonic acid (101), gamma-oxo-benzenepanonic acid methyl ester (102), 3-(2,5-dihydro-4-(hydroxy-5-oxo-3-phenyl-2-furyl)propionic acid (103), (3R)-5-methylmellein (104), Integracins A (105), and B (106) (Figure 7) were isolated from Cytospora sp., of Ilex canariensis from Gomera. Compounds (96–106) are active against B. megaterium, zone size range 15–25 mm when 50 μL of a solution (0.05 mg/mL substance) are pipetted onto 9 mm a sterile filter paper disc (Lu et al., 2011).

Chaetoglobosin B (107) (Figure 8), isolated from the endophyte Chaetomium globosum from the leaves of Viguiera robusta showed weak antibacterial activity against S. aureus (MIC 120 μg/mL) and E. coli (MIC 189 μg/mL) (Momesso et al., 2008).

Chaetoglobin A-B (108–109) (Figure 8) isolated from Chaetomium globosum strain IFF-E036, an endophyte from Cynodon doxylon have antimicrobial activity against B. subtilis, Streptococcus pyogens, Micrococcus luteus and Mycobacterium smegmatis with MICs between 8 and 32 μg/mL (Ge et al., 2011).

Antibacterial compounds Acremonisol A (110), Semicochliodinol A (111), Cochliodinol (112), were isolated...
FIGURE 5 | Structures of antibacterial metabolites isolated from Ascomycetes (65–79).

from *C. globosum* SNB-GTC2114 and Pyrrocidine A (113), B (114), C (115), and Alterperylenol (116) (Figure 8) were isolated from *Lewia infectoria* SNB-GTC2402 obtained from *Besleria insolita* from the Amazon Rainforest biome of Cayenne and Roura, French Guiana. Compounds (110–112, 115, and 116), exhibited antibacterial activity against *S. aureus* ATCC 29213 with MICs of 64, 2, 4, 2, and 32 μg/mL respectively. Compounds (113–114) were active against *S. aureus* ATCC 29213, with a MIC value of 5 μg/mL (Casella et al., 2013).
7-amino-4-methylcoumarin (117) (Figure 8) was isolated from the endophyte Xylaria sp., of Ginkgo biloba. The compound showed strong antibacterial against S. aureus, E. coli, S. typhi, Salmonella typhimurium, Salmonella enteritidis, Aeromonas hydrophila, Yersinia sp., Vibrio anguillarum, Shigella sp., and Vibrio parahaemolyticus with MIC of 16, 10, 20, 15, 8.5, 4, 12.5, 25, 6.3, and 12.5 μg/mL respectively (Liu et al., 2008).

1-(xylarenone A)xylariate A (118), Xylarioic acid B (119) (Figure 8), Xylariolide A (120), Xylariolide B (121), Xylariolide...
C (122), Me-xyxariate C (123), Xylariolide D (124), and tawypyrone (125) (Figure 9), were isolated from Xylaria sp.NCY2 of Torreya jackii Chun collected from Jiangshi Nature Reserve Zone of Fujian Province, China. Compounds (118–125) are active against E. coli ATCC 25922, B. subtilis ATCC 9372 and S. aureus ATCC 25923 with MIC values above 10 μg/mL (Hu et al., 2010).

The polyketide, Cryptosporioptide (126) (Figure 9) was isolated from a Cryptosporiopsis sp., from the shoot tissues of the shrub Viburnum tinus, collected from Gomera. At 50 μg per
FIGURE 8 | Structures of antibacterial metabolites isolated from Ascomycetes (107–119).
FIGURE 9 | Structures of antibacterial metabolites isolated from Ascomycetes (120–139).
Monocerin (127), (125)-12-hydroxymonocerin (128) and Isocoumarin (129) were isolated from Microdochium bolleyi, an endophyte from Fagonia cretica. All these compounds were active against E. coli and B. megaterium (Zhang et al., 2008a).

Isofusidienol A (130), B (131), C (132), and D (133) (Figure 9) were isolated from a Chalara sp. strain 6661, an endophyte of Artemisia vulgaris, collected from Ahrenshoop, Germany. Compounds (130) and (131) showed strong antibacterial activities against B. subtilis with inhibition zones of 23 and 22 mm respectively, at 15 μg of compounds per 6-mm filter disks. Under the same conditions, 15 μg of Penicillin G has a zone of 50-mm diameter. The MIC of compound (130) was shown to be 0.625 μg on 6-mm filter disks. Compound (130) shows moderate activity against S. aureus and E. coli with an inhibition zone diameter of 9 and 8 mm, respectively, at 15 μg of compound per 6-mm filter disk. Compound (132) and (133) show inhibition zone of 9 and 8 mm against B. subtilis at 15 μg per 6-mm filter disk (Loesgen et al., 2008).

Secalonic acid B (134), Blnenolides A (135) and B (136) (Figure 9) were isolated from a Blemoria sp., an endophyte of Carpobrotus edulis, from El Cedro, Gomera. Compounds (134–136) inhibit B. megaterium, and compounds (135) and (136) also inhibited E. coli (Zhang et al., 2008b).

Spiropreussiae A (137) (Figure 9) was obtained from an endophyte, Preussia sp., of the mature stems of Aquilaria sinensis (Thymelaeaceae), collected from the Guangxi Medicinal Arboretum. Spiropreussiae A (137) shows activity against S. aureus (CMCC B26003) with a zone of inhibition of 16.4 ± 0.3 mm (n = 3) at 5 μg/disk. The MIC of the compound in agar dilution test using NCCLS 2002 guide lines was 25 μM (Chen et al., 2009).

Monomethylsulochrin (138), Rhizotonic acid (139), (Figure 9) and Guignasulfide (140) (Figure 10) were isolated from a Guignardia sp. IFB-E028, an endophyte of Hopea hainanensis and show moderate activity against the human bacterial pathogen Helicobacter pylori with MIC values of 28.9, 60.2, and 42.9 μM, respectively (Wang et al., 2010).

Helvolic acid (141) (Figure 10) was isolated from the endophyte Pichia guilliermondii Pp9 of medicinal plant Paris polyphylla var. yunnanensis. Compound (141) has strongest antibacterial activity on Agrobacterium tumefaciens, E. coli, Pseudomonas lachrymans, Ralstonia solanacearum, Xanthomonas vesicatoria, B. subtilis, S. aureus, and Staphylococcus haemolyticus, with MICs of 1.56, 3.13, 3.13, 1.56, 3.13, 50, and 6.25 μg/mL, respectively (Zhao et al., 2010).

Chlorogenic acid (142) (Figure 10) was isolated from the endophyte strain B5 a Sordariomycete sp. of Eucommia ulmoides. Eucommia ulmoides is a medicinal plant of China and one of the main sources of Chlorogenic acid. It has antibacterial, antifungal, antioxidant and antitumor activities (Chen et al., 2010).

Antibacterial Biscogniauxaphilones A (143) and B (144), N-trans-feruloy-3-O-methylidopamine (145), 5-Hydroxy-3,7,4-trimethoxyflavone (146), 4-Methoxycinnamaldehyde (147), Methyl 3,4-methylenedioxyinnamate (148), 4-Methoxytrans-cinnamic acid (149), (Figure 10) were isolated from the endophyte Biscogniauxia formosana BCRC 33718, of Cinnamomum sp. Compounds (143) and (144) show antmycobacterial activities against M. tuberculosis strain H37Rv in vitro showing MIC values of ≤5.12 and ≤2.52 μg/mL, respectively, than the clinical drug Ethambutol (MIC 6.25 μg/mL). Compounds (145–149) show moderate to weak antmycobacterial activities with MICs of 12.5, 25.0, 42.1, 58.2, and 50.0 μg/mL, respectively (Cheng et al., 2012).

Dothideomycetide A (150) (Figure 10) from an endophyte a Dothideomycete sp., of a Thai medicinal plant, Tilia cordata, has antibacterial activity against S. aureus ATCC 25923 and MRSA ATCC 35991 with MIC values of 128 and 256 μg/mL respectively (Senadeera et al., 2012).

Cristatamins A (151) and Tardioxopiperazine A (152) (Figure 10) were produced by the endophyte Eurotium cristatum EN-220 of marine alga Sargassum thunbergii and showed activity against E. coli and S. aureus with MIC values of 64 and 8 μg/mL, respectively (Du et al., 2012).

**COMPOUNDS PRODUCED BY HYPOCHOMYCETES**

Hyphomycete form a class of fungi which produces the assexual spores. Producers of the antibacterials Penicillins and Cephalosporins belong to this class. Other antibacterials from this class are Helvolic acid (141) (Figure 10), Monomethylsulochrin (138) (Figure 9), Ergosterol (79) (Figure 5) and 3β-Hydroxy-5α, 8α-epidioxy-ergosta-6,22-diene (153) (Figure 11) were isolated from an endophyte Aspergillus sp. CY725 of Cynodon dactylon (Poaceae). Compounds (141), (138), (79), and (153) are active against H. pylori with MICs of 8.0, 10.0, 20.0, and 30.0 μg/mL respectively. Helvolic acid (141) is active against Sarcina lutea and S. aureus with MICs of 15.0 and 20.0 μg/mL respectively (Li et al., 2005).

Aspergicin (154) and Neoaspergic acid (155) (Figure 11) were isolated from a mixture of cultured mycelia of two marine-derived mangrove epiphytic Aspergilli FSY-01 and FSW-02. Aspergicin (154) has anti-bacterial activity against S. aureus, S. epidermidis, B. subtilis, B. dysenteriae, B. proteus, and E. coli, with MICs of 62.5, 31.25, 15.62, 15.62 62.5, and 31.25 μg/mL respectively. Neoaspergic acid (155) has antibacterial activity against S. aureus, S. epidermidis, B. subtilis, B. dysenteriae, B. proteus, and E. coli, with MICs of 0.98, 0.49, 1.95, 7.8, 7.8, and 15.62 μg/mL respectively (Zhu et al., 2011).

Two new dihydroisocoumarin derivatives Aspergillumarin A (156) and B (157) (Figure 11) are produced by a marine-derived Aspergillus sp., of the mangrove Brugiaera gymnorrhiza collected from the South China Sea. Both show weak antibacterial activities against S. aureus and B. subtilis at 50 μg/mL (Li et al., 2012).

Brevianamide M (158), 6, 8-di-O-methylverufin (159) and 6-O-Methylerufin (160) (Figure 11), were isolated from Aspergillus versicolor a fungus of the marine brown alga Sargassum thunbergii. These compounds have activities against S. aureus and E. coli (Miao et al., 2012).

Isorhodomitrin-1-Me ether (161), Siderin (162) (Figure 11), were isolated from the marine fungus Aspergillus versicolor of inner tissues of the Red Sea green alga Halimeda opuntia. Both the compounds show moderate activity against

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FIGURE 10 | Structures of antibacterial metabolites isolated from Ascomycetes (140–152).
Bacillus cereus, B. subtilis, and S. aureus at a concentration of 50 μg/disc of 9 mm (Hawas et al., 2012).

Yicathin B (163) and C (164) (Figure 11) were isolated from the endophyte Aspergillus wentii PT-1 of the red marine alga Gymnogongrus flabelliformis. Tested in the agar diffusion assay at 10 mg/disk compound (163) was active against E. coli (inhibition zone diameter 9 mm) and (164) a zone diameter of 12.0 mm and against S. aureus 7.5 mm (Sun et al., 2013b).

The alkaloids, Fumigaclavine C (165) (Figure 11) and Pseurotin A (166) (Figure 12) were isolated from the endophyte
FIGURE 12 | Structures of antibacterial metabolites isolated from Hyphomycetes (166–177).

Pseurotin A (166)

Sclerotiorin A (167)

Emodin (168)

Erythritol (169)

Conidiogenone B (170)

Conidiogen (171)

3,1'-didehydro-3[2''(3''',3'''-dimethyl-prop-2-enyl)-3''-indolymethylene]-6-methyl piperazine-2,5-dione (172)

Perinadine A (173)

Alternariol (174)

Citrinin (175)

X-Y = CH₂CH₂, (2S,2'R,3R,3'E,4E,8E,10E)-1-O-beta-D-glucopyranosyl-2-N-(2'-hydroxy-3'-octadecenoyl)-3-hydroxy-9-methyl-4,8,10-sphingatrienine (176)

X-Y = CH = CH (2S,2'R,3R,3'E,4E,8E)-1-O-beta-D-glucopyranosyl-2-N-(2'-hydroxy-3'-octadecenoyl)-3-hydroxy-9-methyl-4,8-sphingadienine (177)

FIGURE 12 | Structures of antibacterial metabolites isolated from Hyphomycetes (166–177).
Aspergillus sp. EJC08, of the medical plant Bauhinia guianensis. Fumigaclavine C (165) has activity against B. subtilis, E. coli, P. aeruginosa, and S. aureus with MICs of 7.81, 62.50, 31.25, and 15.62 μg/mL respectively, while Pseurotin A (166) has activity against B. subtilis, E. coli, P. aeruginosa, and S. aureus with MICs of 15.62, 31.25, 31.25, and 15.62 μg/mL respectively (Pinheiro et al., 2013).

Pseurotin A (166) (Figure 12) was isolated from Penicillium janczewskii of the Chilean gymnosperm Prumnopitys andina. The compound shows moderate activity against phytopathogenic bacteria Erwinia carotovora and Pseudomonas syringae, with IC50 values of 220 and 112 μg/mL, respectively (Schmeda-Hirschmann et al., 2008).

(+)-Sclerotiorin (167) (Figure 12), was isolated from the endophyte Penicillium sclerotiorum PSU-A13 (Arunpanichlert et al., 2010). Compound (167) has been reported to have antibacterial activity against S. aureus ATCC 29213 (MIC 128 μg/mL) (Lucas et al., 2007).

Emodin (168) and Erythritol (169) (Figure 12) were isolated from the endophyte Penicillium citrinum strain ZD6 of the stems of Bruguiera gymnorrhiza. Emodin (168) and Erythritol (169) inhibit the growth of B. subtilis with MIC values of 25 μg/mL and 50 μg/mL respectively, while Emodin (168) was weakly active against P. aeruginosa at an MIC value of 100 μg/mL (Li et al., 2010).

Antibacterial Conidiogenone B (170) and Conidiogenol (171) (Figure 12) were isolated from Penicillium chrysogenum QEN-24S, an endophyte of a marine red algal species of the genus Laurencia. Conidiogenone B (170) has potent activity against MRSA, Pseudomonas fluorescens, P. aeruginosa, and S. epidermidis (at a concentration of 8 μg/mL), while Conidiogenol (171) is activity against P. fluorescens and S. epidermidis (both at an MIC value of 16 μg/mL) (Gao et al., 2011).

(3, 1’-didehydro-3’β (3’α, 3’β’-dimethyl-prop-2-enyl)-3’β-indolylmethylen)-6-Mepipera-zene-2, 5-dione (172) (Figure 12) was isolated from Penicillium chrysogenum MTCC 5108, an endophyte of the mangrove plant Porteresia coarctata (Roxb.), which has significant activity against Vibrio cholerae MCM B-322 (Devi et al., 2012).

Perinadine A (173), Alternariol (174), and Critinin (175) (Figure 12) were isolated from Penicillium citrinum present on the flowers of Ocinum tenuiflorum (Lamiaceae) collected in Denpasar, Bali, Indonesia. Compounds (173-175) were moderately active against S. aureus ATCC 29213 (MICs 64 μg/mL). These compounds, failed to inhibit the col. E. coli ATCC 25922, and P. aeruginosa B 63230 at 64 μg/mL (Lai et al., 2013).

Fusarides (2S,2′R,3R,3′E,4E,8,10E)-1-0-β-D-glucopyranosyl-2-N-(2′-hydroxy-3′-octadecenoyl)-3-hydroxy-9-methyl-4,8, 10-sphingatirine (176), (2S,2′R,3R,3′E,4E,8,10E)-1-0-β-D-glucopyranosyl-2-N-(2′-hydroxy-3′-octadecenoyl)-3-hydroxy-9-methyl-4,8-sphingadienine (177) (Figure 12) were isolated from a Fusarium sp. IFB-121, an endophyte of Quercus variabilis. Both cerebrosides have strong antibacterial activities against B. subtilis, E. coli and P. fluorescens with MIC values of 3.9, 3.9 and 1.9 μg/mL and 7.8, 3.9, and 7.8 μg/mL respectively (Shu et al., 2004).

Fusapyridon A (178) (Figure 13) was isolated from Fusarium sp. YG-45, an endophyte of the stem of Maackia chinesis, collected at Gottingen (Germany). The compound is active against P. aeruginosa and S. aureus, with MIC values of 6.25 and 50 μg/mL respectively (Tsukinari et al., 2007).

Beauvericin (179) (Figure 13) was found in the endophyte Fusarium redolens Dzf2, of the rhizomes of Dioscorea zingiberensis. The IC50 values of Beauvericin against six test bacteria viz. B. subtilis, Staphylococcus hemolyticus, Pseudomonas lachrymans, Agrobacterium tumefaciens, E. coli and X. vesicatoria were between 18.4 and 70.7 μg/mL (Xu et al., 2010b). Beauvericin and (−)-4, 6′-anhydro-oxysporidinone (180) (Figure 13) were isolated from the endophyte Fusarium oxysporum of the bark of Cinnamomum kanehirae from Jiaoban Mountain, Taiwan Province. Beauvericin (179) is active against MRSA and B. subtilis at MICs of 3.125 μg/mL. (−)-4, 6′-anhydro-oxysporidinone (180) has weak anti-MRSA activity (MIC, 100 μg/mL) and moderate activity against B. subtilis (MIC, 25 μg/mL) (Wang et al., 2011).

Javanicin (181), 3-O-methylfusarubin (182), a diastereomer of Dihydropapthalenone (183) and 5-Hydroxy-3-methoxydihydrofusarin A (184) (Figure 13) were isolated from the endophyte Fusarium sp. BCCI4842 of Bamboo leaf, collected from the Bamboo forest at Nam Nao National Park, Phetchabun Province, Thailand. Compound (181), and (183) have moderate activities (MICs of 25 μg/mL) while 3-O-methylfusarubin (182) and 5-hydroxy-3-methoxydihydrofusarin A (184) showed weak antimycobacterial activity (MICs of 50 μg/mL) (Kornsakulkarn et al., 2011).

Fusaric acid was obtained from a Fusarium sp. an endophyte of a mangrove plant. Cadmium and Copper metal complexes were prepared. The Cadmium (185) and Copper (186) (Figure 13) complexes of fusaric acid exhibited potent inhibitory activity against the Mycobacterium bovis BCG strain with MIC 4 μg/mL and the M. tuberculosis H37Rv strain with MIC 10 μg/mL respectively (Pan et al., 2011).

Fumitermorgin B (187), Fumitermorgin C (188), Helvolic acid (141), Bisdsethiobis (methylthio) gliotoxin (189) (Figure 13), Bis-N-norgliovietin (190) and Gliotoxin (191) (Figure 14) were isolated from the endophyte Fusarium solani of Ficus carica. All compounds are active against B. subtilis, S. aureus, and E. coli and P. aeruginosa with MICs in the range of 0.5–16 μg/mL. (Zhang et al., 2012).

Lateropyrone (192), Enniatins B1 (193) and A1 (194) (Figure 14), were isolated from mix culture fermentation of the fungal endophyte Fusarium tricinctum and the bacterium B. subtilis 168 trpC2 on solid rice medium. Fusarium tricinctum was obtained from rhizomes of Aristolochia paucinervis of the mountains of Beni-Mellal, Morocco. Enniatins B1 (193) and A1 (194), inhibit the growth the B. subtilis strain (MICs of 16 and 8 μg/mL, respectively) and were also active against S. aureus, S. pneumoniae, and E. faecalis with MIC values in the range 2–8 μg/mL. Lateropyrone (192) has antibacterial activity against B. subtilis, S. aureus, S. pneumoniae and E. faecalis, with MICs values ranging from 2 to 8 μg/mL. All the above compounds were equally effective against a multi-drug-resistant clinical isolate of S. aureus (Ola et al., 2013).
FIGURE 13 | Structures of antibacterial metabolites isolated from Hyphomycetes (178–189).
FIGURE 14 | Structures of antibacterial metabolites isolated from Hyphomycetes (190–204).
Rhein (195) (Figure 14) was isolated from an endophyte Fusarium solani of Rheum palmatum collected at Ruogai County, Sichuan Province, China. Rhein (195) naturally occurs in antrahuquinone (1, 3, 8-trihydroxy-6-Me antrahuquinone), that is found in Rheum palmatum L. and related plants such as rhubarb (You et al., 2013). It has good antibacterial activity with MICs in the range of 0.6–4 μg/mL against S. aureus, S. aureus nor A, B. megaterium 11561, Staphylococcus aureus and against MRSA and E. coli (MIC 0.5 μg/mL) (Shang et al., 2012).

Sanguinarine (196) (Figure 14), a benzophenanthridine alkaloid was obtained from the endophyte Fusarium proliferatum (strain BLH51) present on the leaves of Macleaya cordata of the Dabie Mountain, China. It has antibacterial, antihelmintic, and anti-inflammatory activities (Wang et al., 2014). It has antibacterial activities against the range of bacteria with MICs of 3.12–6.25 μg/mL against 15 clinical isolates of S. aureus while the MICs against of the two reference strains are 3.12 μg/mL for ATCC 25923 and 1.56 μg/mL for ATCC 33591.

The clinical isolates strains showed MIC values ranging from 31.25 to 250 μg/mL for ampicillin and 125–1000 μg/mL for ciprofloxacin. The treatment of the cells with sanguinarine induced the release of membrane-bound cell wall autolytic enzymes, which eventually resulted in lysis of the cell. Transmission electron microscopy (TEM) of MRSA treated with Sanguinarine show alterations in septa formation. The predisposition of lysis and altered morphology seen by TEM indicates that sanguinarine acts on the cytoplasmic membrane (Obiang-Obounou et al., 2011). The compound also has activity against plaque bacteria with MICs of 1–32 μg/mL for most species tested. The Electron microscopic studies of bacteria exposed to sanguinarine show that they aggregate and become morphologically irregular (Godowski, 1989).

Shikimic acid (197) (Figure 14), was obtained from the endophyte Trichoderma ovalisporum strain PRE-5 of the root of the herbal Panax notoginseng. The compound (197) is activity against S. aureus, Bacillus cereus, M. luteus and E. coli (Dang et al., 2010).

Trichoderic acid (198), 2β-Hydroxytrichoraconin (199), Cyclonerodiol (200), Cyclonerodiol oxide (201), and Sorbicillin (202) (Figure 14), were isolated from a Trichoderma sp. PR-35, an endophyte of Paecilomyces delavayi. These compounds are active against E. coli and S. albus with minimal inhibitory amount (MIA) values in the range of 25–150 mg/disk. Compounds (198), (200) and (201) are active against Shigella sonnei with MIA values in the range of 100–150 μg/disk (Wu et al., 2011).

Cyclopeptides PF1022F (203) and Halobacillin (204) (Figure 14), were isolated from the endophyte Trichoderma asperellum from traditional Chinese medicinal plant Panax notoginseng. Compounds (203) and (204) are active against E. faecium (CGMCC 1.0253) with IC₅₀ values of 7.30 and 5.24 μM and against S. aureus COL (CGMCC 1.2465) with IC₅₀ values of 19.02 and 14.00 μM, respectively (Ding et al., 2012).

Tetraydrobostyrin (205), 4-Deoxytetraydrobostyrin (206), 3,6,8-Trihydroxy-1- methylxanthone (207), Grisocoponene C (208) and 2,3-Didehydro-19α-hydroxy-14-epicocchiquinone B (209) (Figure 15), were isolated from the endophyte Nigrospora sp. MA75, of the mangrove plant Pongamia pinnata collected from Guangxi Zhuang Autonomous Region of China. Compound (209) has excellent activity against all the tested bacteria (MRSA, E. coli, P. aeruginosa, P. fluorescens and S. epidermidis) with MIC values of 8, 4, 4, 0.5, and 0.5 μg/mL, respectively. The activity toward E. coli, P. fluorescens and S. epidermidis was stronger than that of the positive control (Ampicillin, with MICs values of 8, 4, and 4 μg/mL, respectively). Compound (208) strongly inhibits MRSA, E. coli, P. aeruginosa, and P. fluorescens at MIC values of 0.5, 2, 0.5, and 0.5 μg/mL, respectively. Compound (205) has significant activity toward MRSA and E. coli (MIC 2 and 0.5 μg/mL, respectively), while its analog compound (206), is only activity against E. coli (MIC 4 μg/mL). This indicates that the OH group at C (4) could be important for the activity against MRSA. Compound (207) is active only against S. epidermidis (MIC 0.5 μg/mL) (Shang et al., 2012).

4-Deoxybostyrin (210) and its derivative Nigrosporin (211) (Figure 15), were isolated from the mangrove endophyte Nigrospora sp. of the South China Sea. These compounds are active against M. tuberculosis and clinical multidrug-resistant (MDR) M. tuberculosis strains with MIC values of <5–> 60 μg/mL (Wang et al., 2013b).

Periconicins A (212) and B (213) (Figure 15), were isolated from an endophyte Periconia sp., from the branches of Taxus cuspidata. Periconicin A (212) has significant activity against B. subtilis, S. aureus, K. pneumoniae, and Salmonella typhimurium with MICs in the range of 3.12–12.5 μg/mL. Periconicin B (213) has modest antibacterial activity against the same strains with MICs in the range 25–50 μg/mL (Kim et al., 2004).

Piperine (214) (Figure 15), which was originally isolated from Piper longum, was also detected from the endophyte Periconia sp. of the same plant. Piperine has strong activity against M. tuberculosis and M. smegmetis with MICs of 1.74 and 2.62 μg/mL respectively (Verma et al., 2011).

Modiolide A, 5, 8-dihydroxy-10-methyl-5, 8, 9, 10-tetrahydro-2H-Oxecin-2-one (215) and 4-Chromanone, 6-hydroxy-2-methyl- 5SC (216) (Figure 15) were isolated from the endophyte Periconia siamensis (strain CMUGE015) of the leaves of the grass, Thysanoleana latifolia (Poaceae). Compound (215) is active against Bacillus cereus, Listeria monocytogenes, MRSA, P. aeruginosa and E. coli with MIC of 3.12, 6.25, 25.00, 12.50, and 50.00 μg/mL respectively. Compound (216) is active against B. cereus, Listeria monocytogenes, MRSA, P. aeruginosa and E. coli with MICs of 6.25, 12.50, 50.00 25.00, 12.50, and 100.00 μg/mL respectively (Bhilabutra et al., 2007).

Xanalteric acids I (217) and II (218) (Figure 15) and Altenusin (219) (Figure 16), were obtained from Alternaria sp., of the mangrove plant Sonneratia alba. These (217–218) has weak antibacterial activities against MRSA with MICs of 125 and 250 μg/mL. Altenusin (219) exhibited broad antimicrobial activity against several resistant pathogens (MRSA, S. pneumoniae, E. faecium, E. cloacae and A. faecalis) with MIC values of 31.25–125 μg/mL (Kjer et al., 2009).

1-(2, 6-dihydroxyphenyl) butan-1-one (220) (Figure 16), was isolated from the endophyte Nodulisporium sp. of Juniperus cedrus from Gomera Island. Compound (220) is active against B. megaterium at 0.25 μg/filter disc with 15 mm zone of inhibition (Dai et al., 2006).
Nodulisporins D-F (221–223), Benzene-1, 2, 3-triol (224) (Figure 16), were isolated from an endophyte Nodulisporium sp. of Erica arborea. Compounds (221–224) showed activity against B. megaterium (Dai et al., 2009b).

Pyrrocidine (113) (Figure 9), was isolated from Acremonium zeae an endophyte of maize. Compound (113) has potent activity against Clavibacter michiganense subsp. Nebraskense a causal agent of Goss’s bacterial wilt of maize (MICs 1–2 μg/mL), as well as Bacillus mojavensis (MICs 1–2 μg/mL) and P. fluorescens (MICs 1–2 μg/mL) (Wicklow and Poling, 2009).

Rhizoctonic acid (139), Monomethylsulochrin (138) (Figure 9), Ergosterol (79) (Figure 5) and 3β, 5α, 6β-trihydroxyergosta-7, 22-diene (225) (Figure 16), were isolated from a Rhizoctonia sp. (Cy064), the endophyte in the leaves of Cynodon dactylon. Compounds (139, 138, 79, and 225) are active against five clinical and one reference strain of H. pylori (ATCC
FIGURE 16 | Structures of antibacterial metabolites isolated from Hyphomycetes (219–232).

R₁=R₂=R₃=H, (R)-(-)-mellein (229)
R₁=R₃=H, R₂=OH, cis-(3R,4R)-(−)-4-hydroxymellein (230)
R₁=OH, R₂=R₃=H, trans-(3R,4S)-(−)-4-hydroxymellein (231)
R₁=R₂=R₃=H, R₃=OH, (R)-(−)-5-hydroxymellein (232)
with MICs in the range 10.0–30.0 μg/mL (Ma et al., 2004).

Ophiobolins P (226) and T (227) (Figure 16), were isolated from the endopholic fungus *Ulocladium* sp. Ophiobolins P has moderate antibacterial activity against *B. subtilis* and MRSA with MICs of 62.5 and 31.3 μg/mL respectively. Ophiobolin T (227) has moderate activity against *B. subtilis* and MRSA and Bacille Calmette-Guerin strain with MICs of 31.3 15.6 and 31.3 μg/mL respectively (Wang et al., 2013a).

The antibacterial naphthquinone lavanicin (181) (Figure 13) was isolated from an endophyte *Chloridium* sp. of *Azadirachta indica*. This compound is very active against *P. fluorescens* and *P. aeruginosa* with MIC of 2 μg/mL (Khrarrow et al., 2009).

(3R)-Lasioioplinol (228), (R)-(−)-Mellein (229), Cis-(3R, 4R)-(−)−4-Hydroxymellein (230), trans-(3R, 4S)-(−)−4-Hydroxymellein (231), (R)-(−)−5-Hydroxymellein (232) (Figure 16) were isolated from the endophyte *Botryosphaeria rhodina* PSU-M35 and PSU-M114. Compound (228) is very active against *S. aureus* and MRSA with MIC values of 64 and 128 μg/mL respectively. Compounds (229–232) have much weaker activities than compound (228) with MIC values > 128 μg/mL (Rukachaisirikul et al., 2009).

Fusidilactones D (233) and E (234) (Figure 17) were isolated from the endophyte, a *Fusidium* sp. from the leaves of *Daphnopsis americana* growing in Guanacaste, Costa Rica, may prove to belong to potentially new class of antibacterial agents with activities against MRSA and VRE (Singh et al., 2000). Guanacastepene I (244) (Figure 18), was isolated from the same fungus is active against *S. aureus* (Brady et al., 2001).

Anhydrofusarubin (245) (Figure 18), was isolated from the endophyte no. B77 of a mangrove tree on the South China Sea coast. Compound (245) is active against *Staphylococcus aureus* (ATCC27154) with a MIC of 12.5 μg/mL (Shao et al., 2008b).

Ophiobolin N (239) (Figure 13), Fusarubin (246) (Figure 18), were isolated from the endophyte B77 present in the seeds of the mangrove plant *Kandelia candel* in Zhanjiang. Compounds (182) and (246) were active against *S. aureus* ATCC 27154 with MIC values of 50.0 and 12.5 μg/mL respectively (Shao et al., 2008a).

Compound (247), 3R,4R−Hydroxyhalorosellinia A (248) and Desoxybostrycin (249) (Figure 18), were isolated from the endophyte PSU-N24 present in the plant *Garcinia nigrolineata* collected from the Ton Nga Chang wildlife sanctuary, Songkhla province, southern Thailand. Compound (248) was active against *M. tuberculosis* with the MIC value of 12.50 μg/mL whilst compounds (247) and (249) had MIC values of 25 and 50 μg/mL, respectively (Sommart et al., 2008).

Indolyl-3-carboxylic acid (250) (Figure 18), isolated from the endophyte S20 of *Cephalotaxus hainanensis* Li. showed inhibition of *S. aureus* and MRSA with diameters of inhibition zones of which were 12 and 8 mm, respectively when 50 μL of the compound (10 mg/mL) impregnated on sterile filter paper discs (6-mm diameter) (Dai et al., 2009a). The structure of a new 5-acetyl-2-methylpyrrole (251) (Figure 18) from the same endophyte S20 of *Cephalotaxus hainanensis*, was shown to be 1-(5-methyl-1H-pyrrol-2-yl)-2-((2S*, 3R*)-3-((E)-prop-1-enyl) oxiran-2-yl) ethanone. Compound (251) is active against *S. aureus* and MRSA. The diameters of inhibition are 12.0 mm and 10.0 mm respectively when 50 μL (10 mg/mL) of the compound was impregnated on sterile filter paper discs (6-mm diameter) (Dai et al., 2009c).

Spirobisnaphthalenes, namely Diepoxin k (252), Diepoxin η (253), and Diepoxin z (254) (Figure 18), were isolated from the endophyte Dzf12 of the medicinal plant *Dioscorea zingiberensis*. Among these, compound (252) has antibacterial activity, against *E. coli*, *A. tumefaciens*, *X. vesicatoria*, *P. lachrymans* and *B. subtilis* with MICs from 50 to 100 μg/mL. A mixture of diepoxin η (253), and diepoxin z (254) showed antibacterial activity against the same set of bacteria with a MICs range of 5.0–12.5 μg/mL (Cai et al., 2009).

4-Hydroxyphthalalde (255), 5-methoxy-7-hydroxyphthalalde (256), (3R, 4R)-(−)-4-hydroxymellein (257) (Figure 19), were obtained from an unidentified Ascomycete from *Meliotus daenatus* of the coastal area of the Baltic Sea, Ahrenslopp, Germany. Compounds (255) and (256) were active against *E. coli* whereas (256) and (257) were active against *B. megaterium* (Hussain et al., 2009b).

Pestalothelae E-H (258–261) and Anofinic acid (262) (Figure 19), were obtained from an unidentified ascomycete of *Arbutus unedo*. Compounds (258–262) have antibacterial activity against *E. coli* and *B. megaterium* (Qin et al., 2011).

Guignardone I (263) and Guignardone B (264) (Figure 19), were isolated from an endophyte fungus A1 of the mangrove plant *Syphyphora hydrophyllacea*. Guignardone I (263) shows zones...
FIGURE 17 | Structures of antibacterial metabolites isolated from Hyphomycetes (233–241).

inhibition of 9.0 and 11.0 mm in diameter, using 6 mm filter paper discs toward MRSA and S. aureus at 65 μM, respectively. Guignardone B (264) shows zones of 8.0 mm against MRSA at 65 μM. Kanamycin sulfate, used as positive control (10 μL of 0.08 mg/mL) showed an inhibition zone of 30 mm (Mei et al., 2012).

Mirandamycin (265) (Figure 19) was obtained from isolate 1223-D, an unclassified fungus of twig of Neomiranda angulares of family Asteraceae. It is active against E. coli 25922, P. aeruginosa 27853, K. pneumoniae carbapenemase positive BAA-1705, MRSA BAA-976 and V. cholerae PW357 with MICs of 80, 80, >80, 10, and 40 μg/mL respectively (Ymele-Leki et al., 2012).

Volatile organic compounds from endophytic fungi
Strobel et al. (2001) reported at least 28 volatile organic compounds (VOC) from the xylariaceous endophyte Muscodor albus (isolate 620), of Cinnamomum zeylanicum from Lancetilla Botanical Garden near La Ceiba, Honduras. These VOC’s are mixtures of gasses of five class’s viz. alcohols, acids, esters, ketones and lipids. The most effective were the esters, of which, 1-butanol, 3-methyl-acetate has the highest activity. The VOC’s inhibited and killed certain bacteria, within a period of 1–3 days. Most test organisms were completely inhibited, and in fact killed. These includes Escherichia coli, Staphylococcus aureus, Micrococcus luteus and Bacillus subtilis along with some fungal species.
FIGURE 18 | Structures of antibacterial metabolites isolated from Unidentified fungus (242–256).

Bostrycin (242)

Guanacastepene A (243)

Guanacastepene I (244)

Anhydrofusarubin (245)

Fusarubin (246)

Indolyl-3-carboxylic acid (250)

5-acyl-2-methylpyrrole (251)

Diepoxin κ (252)

Diepoxin η (253)

Diepoxin ζ (254)

R₁=R₂=R₃=R₅=H, R₄=β-H, R₆=OH, Compound 2 (247)
R₁=OH, R₂=R₃=R₅=H, R₄=α-H, R₆=OH, 9α-hydroxyhalorosellinia (248)
R₁=R₂=H, R₃=R₄=double bond, R₅+ R₆=O Desoxybostrycin (249)

R₁=R₂=H, R₃=OH, 4-hydroxyphthalide (255)
R₁=OH, R₂=OMe, R₃=H, 5-methoxy-7-hydroxyphthalide (256)
Strain of *Muscodor* namely *Muscodor crispans* of *Ananas ananassoides* (wild pineapple) growing in the Bolivian Amazon Basin produces VOC’s; namely propanoic acid, 2-methyl-; 1-butanol, 3-methyl-; 1-butanol, 3-methyl-, acetate; propanoic acid, 2-methyl-, 2-methylbutyl ester; and ethanol. The VOC’s of this fungus are effective against *Xanthomonas axonopodis* pv. *citri* a citrus pathogens. The VOC’s of *M. crispans* kill several human pathogens, including *Yersinia pestis*, *Mycobacterium tuberculosis* and *Staphylococcus aureus*. *Muscodor crispans* is only effective against the vegetative cells of *Bacillus anthracis*, but not against the spores. Artificial mixtures of the fungal VOC’s were both inhibitory and lethal to a number of human and plant pathogens, including three drug-resistant strains of *Mycobacterium tuberculosis* (Mitchell et al., 2010). The mechanism of action of the VOC’s of *Muscodor* spp. on target bacteria is unknown. A microarray study of the transcriptional response analysis of *B. subtilis* cells exposed to *M. albus* VOC’s show that the expression of genes involved in DNA repair and replication increased, suggesting that VOC’s induce some type of DNA damage in cells, possibly through the effect of one of the naphthalene derivatives (Mitchell et al., 2010).

**Outlook**

A definite, urgent and worldwide effort is needed to tackle the problems of the populations in third world and developing countries. MRSA, VRE, PRSP, ESCAPE organisms have spread through these countries over the years particularly due to immunocompromised populations. *Mycobacterium tuberculosis* is a major threat! and New and Novel drugs are a must!! Endophytic fungi may be an excellent source of such compounds. These organisms have a vast repertoire of diverse chemicals such as steroids, xanthones, phenols, isocoumarins, perylene derivatives, quinones, furandiones, terpenoids, depsipeptides and cytochalasins (Tan and Zou, 2001; Gunatilaka, 2006; Zhang et al., 2006; Guo et al., 2008).

A major challenge in Drug Discovery Program based on endophytic fungi lies in developing effective strategies to isolating bioactive strains. Strobel and Daisy (2003) suggested that areas of high biodiversity of endemic plant species may hold the greatest potential for endophytes with novel chemical entities. Tropical forests are some of the most bio diverse ecosystems and their leaves are “biodiversity hotspots” (Arnold and Lutzoni, 2007). The selection of plants is crucial. Those with medicinal properties

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**FIGURE 19** | Structures of antibacterial metabolites isolated from Unidentified fungus (257–265).
should be given preference. Metabolites produced by fungi need to be considered with the plant genomics, thus allowing for a more detailed knowledge of biosynthetic pathways. This will also justify the production of metabolites rather than unproven hypotheses.

Identification of endophytic fungi using molecular analyses provides an opportunity to look for broad patterns in bioactivity not only at the genotype or strain level, but at higher taxonomic levels that may in turn assist in focusing on the association of metabolite with the plant.

The endophytic flora of the Indian subcontinent has been explored for their diversity but not enough for their bioactive metabolites. The published work is scanty (Puri et al., 2005; Deshmukh et al., 2009; Khawar et al., 2009; Periyasamy et al., 2014). There is a need for groups from different scientific disciplines (mycologist, chemist, toxicologist, and pharmacologist) to engage in this search process. Enormous natural wealth exists in developed countries with their financial resources and biodiversity rich countries with underdeveloped economy and limited funds. Many be funding agencies need to look at such aspects.

The need of a more and larger collection of fungal endophytes is suggested. Bioactive metabolite metabolites from such collections could yield leads for pharmaceutical and agricultural application.

What emerges is the essential bonding of various discipline of biology and chemistry into cohesive target delivery vehicles.

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