Endophytes: A Gold Mine of Enzyme Inhibitors

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Abstract

Ever since the landmark discovery of paclitaxel from endophytic *Taxomyces andreanae*, plant endophytes have been the fountainheads of bioactive secondary metabolites with potential application in medicine, agriculture, and food industry. In the last two decades, lead molecules with antimicrobial, anticancer, antioxidant, and anti-inflammatory properties have been successfully discovered from endophytic microorganisms. Bioprospecting endophytes for enzyme inhibitors has been an important facet of endophytic research. Several enzyme inhibitors like altenusin, huperzine, camptothecin, and podophyllotoxin have been successfully isolated from endophytic microorganisms. The current chapter partially embodies the research progress on endophytic microorganisms for producing bioactive enzyme inhibitors and their possible use in pharmaceutical industries.

Keywords

Bioactive compounds · Endophytes · Enzyme inhibitors · Plant-microbe interaction

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4.1 Introduction

Development of resistance among pathogenic microorganisms, frequent appearance of life-threatening viruses, and tremendous increase in the incidences of communicable and noncommunicable diseases have drawn attention toward our inadequacy to manage these medical problems. This calls for an urgent need to exploit and utilize novel resources which could provide relief from the current situation (Strobel and Daisy 2003; Strobel et al. 2004). Natural products are metabolites or by-products of plant, animal, or microbial origin. Over the centuries, plants have been the cornerstone of natural products, but in the recent years, microbes associated with plants emerged as a key supplier of analogous and non-analogous bioactive metabolites with high therapeutic potential (Gouda et al. 2016; Meshram et al. 2016a). After the pathbreaking discovery of "Taxol" from *Taxomyces andreanae*, endophytes from various ecological niches of the world have been extensively exploited for obtaining bioactive metabolites having antimicrobial, anticancer, antiviral, and immunosuppressant activities (Zhao et al. 2011; Aly et al. 2011; Kusari et al. 2013). Endophytes are also found to inhibit specific enzymes and are commonly referred to as enzyme inhibitors. Since several diseases are associated with abnormal enzyme activities, the inhibitors bind to the active sites of the enzyme, thereby blocking the reaction that forms the basis of onset of disease. At present, several enzyme inhibitors like allopurinol, camptothecin, etoposides, febuxostat, lovastatins, mevastatin, and orlistat are available in the market (Baikar and Malpathak 2010; Gupta et al. 2015; Kapoor and Saxena 2014; Roy 2017). In the current chapter, we will discuss about the endophytes (including bacteria and fungi) as a novel bioresource of enzyme inhibitors and their possible application in management of several dreadful diseases.

4.2 Endophytes: A Potential Resource of Bioactive Metabolites

Endophytes comprise of an extremely diverse group of microorganisms that are ubiquitous in plants and maintain a symptomless and unobtrusive union with their hosts for at least a period of their life cycle (Stone et al. 2000; Saxena et al. 2015). The literal meaning of endophyte is "inside the plant" (Gr. endon, within; phyton, plants) (Schulz and Boyle 2005). Endophytic fungi are hyperdiverse and it is estimated that more than 1.5 million species may exist (Arnold et al. 2000). Fungal endophytes are more often encountered in comparison to bacterial endophytes. Once the endophyte enters the internal tissue of the host, they assume the latent phase for their entire life cycle or for an extended duration (Aly et al. 2011; Kaul et al. 2012). Their relationship with the host plant ranges from symbiotic, benign commensels, decomposers, to latent pathogens (Promputtha et al. 2007). During the alliance, none of the interacting partner is harmed, and the benefits obtained are solely dependent on the interacting partners. Thus, endophytism is a novel, cost-effective plant-microbe association driven by location and not by function (Kusari

et al. 2012). Endophytes produce a plethora of metabolites to cross talk with its host. These metabolites are produced in order to acquire nutrient and colonization inside the plant tissue and to provide defense against microbial infection (Borges et al. 2009). The bioactive metabolites obtained from endophytes majorly belong to the chemical class of alkaloids, cytochalasins, flavonoids, polyketides, steroids, and terpenoids (Porras-Alfaro and Bayman 2011). The metabolites produced by the endophytes have been found to exhibit various pharmacological properties, majority of which include antimicrobial, antineoplastic, antioxidant, anticancer, anti-inflammatory, antidiabetic, and antidepressant activities (Strobel and Daisy 2003; Strobel et al. 2004; Suryanarayanan et al. 2009; Kusari et al. 2013). Many biologically active metabolites like Taxol, camptothecin, oocydin, cytosporone, isopectacin, etc. have been successfully isolated from endophytic fungi possessing anticancer, antibacterial, antifungal, and antioxidant activities (Table 4.1) (Firakova et al. 2007; Zhao et al. 2011; Elsebai et al. 2014). Furthermore, endophytes were also found to produce various industrially and clinically important enzymes like amylase, cellulose, laccase, lipase, protease, etc. (Correa et al. 2014; Meshram et al. 2016a, b). Thus, endophytic microorganisms are rich source of biologically active metabolites possessing promising applications in agrochemical and pharmaceutical industries (Strobel and Daisy 2003; Kaul et al. 2012; Zilla et al. 2013; Zhang et al. 2015).

4.3 Enzyme Inhibitors

Enzymes are remarkable biological catalyst that efficiently and selectively catalyzes nearly all biochemical reactions inside a living system. Enzymes increase the rate of reaction by lowering the activation energy. Enzymes are highly specific in nature, and they bind only at the active sites of the substrate, ultimately converting them into products. However, due to some malfunctioning in the metabolic process, the level of enzyme activity is altered from the normal range, ultimately leading to serious metabolic disorders like Alzheimer's and Parkinson's disease, diabetes, and gout (Lehninger et al. 2005; Voet et al. 2013; Kapoor and Saxena 2014; Singh and Kaur 2015).

Agents that block or cease enzymatic reactions are known as enzyme inhibitor. These agents amend enzyme activity by combining in a way that influences the binding of substrate or its turnover number (Baikar and Malpathak 2010). Enzyme inhibitors are broadly classified into two categories: reversible and irreversible inhibitors. Reversible inhibitors are further subclassified into three categories: competitive, noncompetitive, and mixed inhibitors (Lehninger et al. 2005; Voet et al. 2013). Since enzymes carry out all the vital biological reactions, enzyme inhibitors are among the most important sought-after pharmaceutical agents. The current arsenal of pharmaceutical drugs largely comprised of enzyme inhibitors. Presently, almost all the therapies for AIDS are based on the suppression of certain vital enzymes (Roy 2017). At present, several enzyme inhibitors like 5-fluorouracil, cephalosporins, lovastatin, orlistat, penicillin, and ritonavir are available in the

Table 4.1 Bioactive secondary metabolites produced by endophytic fungi

S. no.	Bioactive compound	Endophytic fungi	Property	References
Anticancer agent				
1.1.	Paclitaxel	*Taxomyces andreanae*	Anticancer	Stierle et al. 1993
		Pestalotiopsis microspora		Strobel et al. 1996
1.2.	Camptothecin	*Entrophospora infrequens*	Anticancer	Puri et al. 2005
		Fusarium solani		Kusari et al. 2009a
1.3.	Podophyllotoxin	*Phialocephala fortinii*	Anticancer	Eyberger et al. 2006;
		Trametes hirsuta		Puri et al. 2006
4.	Vinblastine and Vincristine	*Fusarium oxysporum*	Anticancer	Kumar et al. 2013
5.	Torreyanic acid	*Pestalotiopsis microspora*	Anticancer	Lee et al. 1996
Antimicrobial agent				
6.	Cytosporones	*Cytospora* sp.	Antibacterial	Brady et al. 2000
7.	Brefeldin A	*Phoma medicaginis*	Antibacterial	Weber et al. 2004
8.	Sassafrins A–D	*Creosphaeria sassafras*	Antibacterial	Quang et al. 2005
9.	Pestaloside	*Pestalotiopsis microspora*	Antifungal	Lee et al. 1995a, b
10.	Cryptocandin A	*Cryptosporiopsis quercina*	Antifungal	Strobel et al. 1999
11.	Enfumafungin	*Hormonema* sp.	Anticandidal	Onishi et al. 2000
12.	Ambuic acid	*Pestalotiopsis microspora*	Antifungal	Li et al. 2001
Antiviral and antiparasitic agent				
13.	Pochonins A–F	*Pochonia chlamydosporia*	Antiviral and antiparasitic	Hellwig et al. 2003
14.	Pestalotheols A–D	*Pestalotiopsis theae*	Anti-HIV	Li et al. 2008
15.	Preussomerin EG1; palmarumycin CP_2, CP_{17}, and CP_{18}; and CJ-12,371	*Edenia* sp.	Antileishmanial	Martínez-Luis et al. 2008
Other important agents				
16.	Pestacin and isopestacin	*Pestalotiopsis microspora*	Antioxidant	Harper et al. 2003
17.	Subglutinol A	*Fusarium subglutinans*	Immunosuppressant	Lee et al. 1995a, b

(continued)

Table 4.1 (continued)

S. no.	Bioactive compound	Endophytic fungi	Property	References
18.	L-783,281	*Pseudomassaria* sp.	Insulin mimetic	Zhang et al. 1999
19.	Emodin	*Thielavia subthermophila*	Hypericin precursor	Kusari et al. 2008
1.20.	Diosgenin	*Cephalosporium* sp.	Cardiovascular therapy	Zhou et al. 2004
		Fusarium oxysporum	Estrogenic effect	Li et al. 2011

market, and hundreds of them are under clinical trials (Gupta et al. 2015; Drawz and Bonomo 2010). Most of the enzyme inhibitors reported to date are of microbial origin; hence in this section we will discuss about few important enzyme inhibitors isolated from endophytic microorganisms.

4.3.1 Angiotensin Converting-Enzyme (ACE) Inhibitors

Hypertension is the major risk factor that leads to various cardiovascular disorders, cirrhosis, and nephrosis. ACE is a vital component of renin-angiotensin system which maintains blood pressure in the body by regulating the volume of fluids. ACE converts inactive angiotensin I into physiologically active angiotensin II which causes an increase in blood pressure by contracting the blood vessels. Therefore, for the treatment of hypertension, it would be reasonable to administrate drug that inhibits ACE. Inhibitors of ACE bind to the active site of ACE enzyme, hence decreasing their action of narrowing the blood capillaries. Thus, ACE inhibitors are being widely used as hypertensive drugs. Several ACE inhibitors like benazepril, captopril, and ramipril are available for clinical use (Steven-Miles et al. 1995; Zhang et al. 2000; Coates 2003; Barbosa-Filho et al. 2006).

Endophytic *Cytospora* sp. isolated from living bark of *Betula alleghaniensis* produces three different phenolics named as cytosporin A (major), cytosporin B (minor), and cytosporin C (minor). These compounds bind to both angiotensin I and II at different levels with different specificities. Maximum inhibition of angiotensin II was shown by cytosporin A with an IC_{50} value of 1.5–3.0 μM. It also inhibited angiotensin I with an IC_{50} value of 25–30 μM. The other two cytosporins were better inhibitors of angiotensin II than angiotensin I. (Table 4.2, Fig. 4.1) (Steven-Miles et al. 1995).

Graphislactone A and botrallin produced by endophytic *Microsphaeropsis olivacea* exhibited moderate ACE inhibitory activity with an IC_{50} values of 8.1 and 6.1 μg/mL, respectively (Hormazabal et al. 2005). Further, *Pestalotiopsis* spp., isolated from *Terminalia arjuna* and *Terminalia chebula*, has also been reported to inhibit ACE with an inhibition greater than 60%. Out of 32 screened *Pestalotiopsis* spp., only 5 species showed ACE inhibition. From these five species, *Pestalotiopsis microspora* was the most potential one followed by *Pestalotiopsis theae* with an IC_{50}

Table 4.2 List of important enzyme inhibitors from endophytic fungi

Enzyme inhibitor	Enzyme	Source	Targeted disease	References
Cytosporin A	Angiotensin-converting enzyme	*Cytospora* sp.	Hypertension	Steven-Miles et al. 1995
Huperzine A	Acetylcholinesterase	*Shiraia* sp.	Alzheimer's disease, Parkinson's disease, Glaucoma	Zhu et al. 2010
Nectriapyrone	Monoamine oxidase	*Erythrina crista-galli*	Neurological, Psychiatric disorders	Weber et al. 2005
Aurovertin B–D	ATPase	*Calcarisporium arbuscula*	Cardiovascular disorders, Ulcers	Mao et al. 2015
Aurasperone A, rubrofusarin B	Xanthine oxidase	*Aspergillus niger*	Gout	Song et al. 2004
Polyhydroxy anthraquinones	Quorum sensing	*Penicillium restrictum*	Bacterial infections	Figueroa et al. 2014
Bipolarisenol	Urease	*Bipolaris sorokiniana*	Rheumatoid arthritis	Khan et al. 2015
Cytonic acids A–B	Protease	*Cytonaema* sp.	Viral infections	Guo et al. 2000
Solanapyrone A	DNA polymerase	*Alternaria solani*	Cancer, viral infections	Mizushina et al. 2001
Altenusin	Trypanothione reductase	*Alternaria* sp.	Trypanosomiasis	Cota et al. 2008
Radicicol	Heat shock protein 90 kD	*Chaetomium chi-versii*	Cancer	Turbyville et al. 2006
Epicocconigrones A	Histone deacetylases	*Epicoccum nigrum*	Cancer	El Amrani et al. 2014
Fusaristatin A	Topoisomerases I and II	*Fusarium* sp.	Cancer	Shiono et al. 2007
Corynesidone A	Aromatase	*Corynespora cassiicola*	Breast cancer	Chomcheon et al. 2009
Peptide	α-Amylase	*Aspergillus awamori*	Diabetes	Singh and Kaur 2015
Peptide	α-glucosidase	*Aspergillus awamori*	Diabetes	Singh and Kaur 2015
Lovastatin	HMG-CoA reductase	*Phomopsis vexans*	Cholesterol inhibitor	Parthasarathy and Sathiyabama 2015
Fustat	Lipase	*Fusarium incarnatum*	Obesity	Gupta et al. 2015 (Patent filing under process)

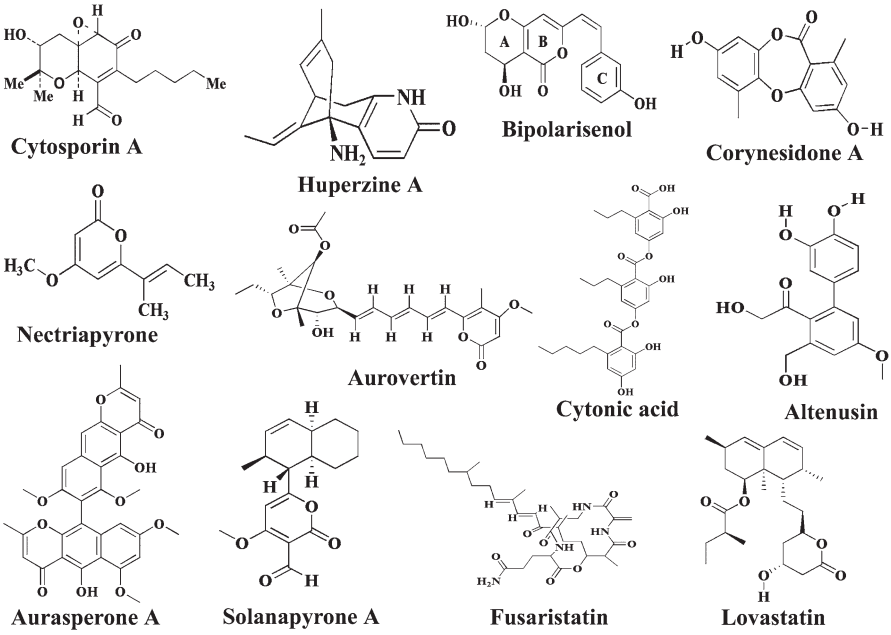

Fig. 4.1 Structures of important enzyme inhibitors from endophytic fungi. (Structures are taken from protologue publications and are redrawn using ChemDraw)

values that range from 21 to 37 μg/mL. These values were quite comparable to captopril (Tejesvi et al. 2008). Thus, it is clearly evident that endophytes are potential but scarcely studied candidates for ACE inhibitors. Hence, there exist immense opportunities to harness endophytic microflora as a novel bioresource of ACE inhibitors.

4.3.2 Acetylcholinesterase Inhibitors

Acetylcholinesterase (AChE) belongs to the family of serine hydrolyses that is primarily found at neuromuscular junctions and cholinergic brain synapses. AChE is majorly involved in termination of impulse transmission at cholinergic synapses by rapid breakdown of AChE into acetate and choline. This reaction is critical because it allows the cholinergic neuron to return back to its latent state after activation (Colovic et al. 2013). The inhibitors of AChE bind at the active site of the enzyme resulting in the accumulation of the acetylcholine at the synapses. Acetylcholinesterase inhibitors (AChEIs) are broadly classified as strong and weak inhibitors. The strong inhibitors comprise of organic phosphates and carbamates which are primarily used as nerve toxins, whereas the weak inhibitors have been employed in the treatment of Alzheimer's disease, autism, dementia, insomnia, and Parkinson's disease. The current arsenal of drugs involved in

treatment of these diseases includes galantamine, huperzine A, donepezil, and rivastigmine. The first two drugs are naturally obtained, whereas the latter ones are chemically synthesized. Even though AChEIs have been obtained from both chemical synthesis and natural resources including plants and microorganisms, the search for alternative avenues for isolating novel AChEIs is still going on (Rodrigues et al. 2005; Su et al. 2017).

The very first attempt to exploit endophytic fungi as a potential source of AChEIs was done by Rodrigues et al. (2005) where they have screened the culture filtrates obtained from the endophytic fungi isolated from Anacardiaceae, Apocynaceae, Leguminosae, and Palmae plant families. The maximum AChE inhibition recorded by these isolates was 43%. Endophytic fungal isolates like *Pestalotiopsis guepini*, *Phomopsis* sp., and *Guignardia mangiferae* displayed selective AChE inhibition, whereas *Chaetomium* and *Xylaria* spp. do not show any inhibitory activity (Rodrigues et al. 2005). Further, endophytic *Alternaria* spp. have been reported to exhibit AChE inhibitory activity. The chloroform extract of endophytic *Alternaria* sp. isolated from the *Ricinus communis* showed a strong AChE inhibitory activity with an IC_{50} value of 40 μg/mL (Singh et al. 2012). Similarly, endophytic *Alternaria alternata* isolated from *Catharanthus roseus* produces "altenuene" which exhibited 78% inhibition of AChE under in vitro conditions. The compound also possessed antioxidant and antilarval activity (Bhagat et al. 2016). Recently, endophytic fungus *Bipolaris sorokiniana* LK12 produces a radicinol derivative, "bipolarisenol," which significantly inhibited AChE with a low IC_{50} value of 67.23 ± 5.12 μg/mL (Khan et al. 2015).

Huperzia serrata is a traditional Chinese medicinal plant producing a lycopodium alkaloid huperzine A, which is a selective and reversible AChEI (Liu et al. 1986a, b). Huperzine A possesses better inhibitory activity than its counterparts donepezil and tacrine owing to its greater half-life, higher oral bioavailability, and lesser known side effects (Zhao and Tang 2002; Zangara 2003; Ma et al. 2007). Endophytic microorganisms possess a special property of synthesizing analogous compounds similar to their host (Saxena et al. 2015). Endophytic fungal isolate *Shiraia* sp. Slf14 associated with *Huperzia serrata* produced 327.8 μg/l of huperzine A which was higher than that from the previously reported endophytic isolates *Acremonium* sp., *Blastomyces* sp., and *Botrytis* sp. Furthermore, huperzine A from *Shiraia* sp. Slf14 exhibited dose-dependent AChE inhibitory activity. About 10 μg/ml of huperzine A from methanolic extract of endophytic fungus showed complete inhibition of AChE which was better than that of commercially available huperzine A under laboratory conditions (Table 4.2, Fig. 4.1) (Li et al. 2007; Ju et al. 2009; Zhu et al. 2010). Similarly, two endophytic *Penicillium* sp. L10Q37 and *Penicillium* sp. LQ2F02 isolated from *Huperzia serrata* produce several AChEIs. Ethyl acetate fraction of both the isolates showed 61 and 66% AChE inhibitory activity. Among the different compounds (S1–S10) produced by the two isolates, the lowest IC_{50} was exhibited by compound S5 (5.23 ± 0.28 μg/ml) under in vitro conditions (Wang et al. 2015). Apart from producing analogous compounds, several other bioactive metabolites were also isolated from *Huperzia serrata*. An endophytic fungal isolate

Aspergillus versicolor Y10 produces prenyl asteltoxin derivatives "avertoxins A–D" which also showed AChE inhibitory activity. Among them, avertoxin B (3) was the major compound showing AChE inhibitory activity with IC_{50} value of 14.9 μM (Wang et al. 2015). Thus, from the above reports, it looks apparent that endophytes are good candidates for the AChEIs. However, looking at the broad diversity of the endophytic microorganisms, various ecological niches around the world need to be exploited in a more rational and precise manner for recovering promising AChEIs with potential therapeutic application.

4.3.3 Monoamine Oxidase Inhibitor

Monoamine oxidase is an intramitochondrial enzyme that catalyzes the oxidative deamination of neurotransmitters such as dopamine, serotonin, and norepinephrine in the central nervous system leading to neurological and psychiatric disorders (Meyer et al. 2006). Low levels of these neurotransmitters lead to anxiety, depression, and schizophrenia (Domino and Khanna 1976). Inhibitors of monoamine oxidase obstruct the action of monoamine oxidase enzyme, thereby increasing the amount of neurotransmitters and thus providing relief from depression and anxiety (Tan et al. 2000). Presently, several monoamine oxidase inhibitors (MOI) including isocarboxazid, selegiline, phenelzine, rasagiline, and tranylcypromine are available in the market for treatment of neurodegenerative conditions. MOI are only used when other antidepressants have failed to work because they suffer from higher risk of drug interaction (Kennedy 1997; Weinreb et al. 2010; Wallach et al. 2017). Since, the currently available MOI also suffer from several drawbacks; the demand for new MOI with fewer side effects is highly desirable.

Weber et al. (2005) documented the production of nectriapyone from extract of *Phomopsis* species. The lead molecule was earlier reported to possess MAO inhibitory activity (Table 4.2, Fig. 4.1) (Lee et al. 1999). Similarly, hypericin is a naturally occurring antidepressant found in several species of *Hypericum perforatum.* Endophytic *Thielavia subthermophila* isolated from *H. perforatum* produces hypericin (Kusari et al. 2008). Metabolites like formamide and furansteroid, produced by endophytic *Talaromyces* sp. isolated from the bark of *Tripterygium wilfordii*, exhibited moderate MAO inhibitory activity (Zhao et al. 2016; Zhi et al. 2016). Further, mullein isolated from the culture broth of *Colletotrichum gloeosporioides* GT-7 exhibited monoamine oxidase inhibitory activity with an IC_{50} value of 8.93 ±0.34 μg/ml (Wei et al. 2016). Furthermore, deacetylisowortmins A and B isolated from an endophytic *Talaromyces wortmannii* LGT-4 also displayed weak monoamine oxidase inhibitory activity (Fu et al. 2016). MOI from endophytic microorganisms are a nascent area with very scanty and preliminary data. However, the available reports suggest that endophytes are prospective microorganisms for isolation of new MOI.

4.3.4 Adenosine Triphosphatase (ATPase) Inhibitors

ATPase is a broad class of enzymes that catalyze the hydrolysis of adenosine triphosphate into adenosine diphosphate and a free phosphate ion, liberating energy which is used for carrying out major biochemical reactions in the body (Chene 2002). ATPase is involved in vital cellular functions like DNA replication and synthesis (Lee and Bell 2000), protein folding and transport (Ranson et al. 1998), and transmembrane ion exchange (Hirokawa et al. 1998; Nishi and Forgac 2002). Several ATPase inhibitors like monastrol, digoxin, benzimidazoles, brefeldin A, sodium orthovanadate, and oligomycin A are already present in the market which play significant role in treatment of diseases like cancer, cardiovascular disorders, gastric disorders, and infections (Chene 2002; Cochran and Gilbert 2005; Sato et al. 2012). This is the reason why ATPase inhibitors hold a special position in pharmacopeia.

Digoxin is a plant glycoside produced by *Digitalis lanata*. The glycosides from this plant possess cardiotonic properties. Kaul et al. (2012) screened 32 endophytic fungal isolates isolated from *Digitalis lanata* and found that 5 isolates showed digoxin production under in vitro conditions. Aurovertin is a fungal polyketide that inhibits ATP synthase. Endophytic *Calcarisporium arbuscula* produces aurovertin B and D which are presently under clinical trial for human use (Table 4.2, Fig. 4.1) (Mao et al. 2015). Aurovertin-type polyketides T and U showed potential cytotoxic activity against triple negative breast cancer (Zhao et al. 2016). Similarly, oligomycin is also an inhibitor of ATP synthase. Neomaclafungins A–I produced by marine-derived actinomycete exhibited strong antifungal activity against *Trichophyton mentagrophytes* with a MIC value between 1 and 3 μg/mL (Sato et al. 2012).

Brefeldin A is a lactone antibiotic and ATPase inhibitor. Endophytic *Cladosporium* sp. isolated from *Quercus variabilis* exhibited brefeldin A production (Wang et al. 2007). Further, endophytic *Paecilomyces* sp. and *Aspergillus clavatus* isolated from *Taxus mairei* and *Torreya grandis* produced brefeldin A which exhibited cytotoxic activity against human tumor cell lines including HL60, KB, Hela, SPC-A-1, and MCF-7 (Wang et al. 2002). Similarly, the ethyl acetate extract of endophytic *Penicillium janthinellum* Yuan-27 also exhibited brefeldin A production which was active against human cancer cell lines like MKN45, LOVO, A549, MDA-MB-435, HepG2, and HL-60 with an IC_{50} value of <0.12 μg/ml (Zheng et al. 2013).

4.3.5 Xanthine Oxidase Inhibitors

Purine catabolism is an enzymatically driven metabolic pathway yielding uric acid as its final product. Xanthine oxidase is a key enzyme of this pathway which catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid. Any impairment in this finely regulated mechanism leads to a condition known as hyperuricemia. Hyperuricemia can be defined as a biochemical abnormality caused due

to high serum urate levels attributed due to overproduction (> 6–7 mg/dl) or underexcretion of uric acid. Further, gout is a common metabolic disorder characterized by chronic hyperuricemia and clinically manifested by unbearable pain in the joints (Lehninger et al. 2005; Voet et al. 2013). Over 4.62 million people across the globe suffer from hyperuricemia or gout. Gout can be prevented by antihyperuricemic therapy involving uricosuric drugs or xanthine oxidase inhibitors (XOI). Among the abovementioned strategies, XOI are more preferred ones, owing to their lesser side effects and interventions with purine catabolism (Kapoor and Saxena 2014, 2016). XOI are of two kinds: purine analogue and non-purine analogue. Purine analogue includes allopurinol, oxypurinol, and tisopurine, whereas non-purine analogue includes febuxostat and inositols (Lehninger et al. 2005). Presently, only allopurinol and febuxostat are clinically approved as XOI. However, there is an increasing demand of new XOI due to side effects encountered by the current drugs (Gu 2009).

Several endophytic fungi have been reported to exhibit XOI activity. Endophytic *Fusarium* sp. IFB-121 isolated from *Quercus variabilis* produced two compounds: a known cerebroside and a fusaruside exhibiting xanthine oxidase inhibitory activity with an IC_{50} values of 55.5 ± 1.8 μM and 43.8 ± 3.6 μM, respectively (Shu et al. 2004). Aurasperone A and rubrofusarin B obtained after fractionation of organic extract of endophytic *Aspergillus niger* IFB-E003 showed profound xanthine oxidase inhibitory activity with the IC_{50} values ranging from 10.9 to 37.7 μmol/l (Table 4.2, Fig. 4.1). The compounds also possessed broad spectrum antimicrobial and anticancer activity (Song et al. 2004). Similarly, endophytic *Chaetomium* sp. isolated from the *Nerium oleander* exhibited xanthine oxidase inhibitory activity with an IC_{50} value of 109.8 μg/mL. The same fungus also showed strong antioxidant activity (Huang et al. 2007). Lumichrome, produced in the liquid culture of endophytic *Myrothecium roridum* IFB-E012, displayed inhibition of xanthine oxidase with an IC_{50} value of 60.32 ± 0.48 μmol/l. The compound also displayed strong cytotoxic activity against human tumor cell line nasopharyngeal epidermoid KB (Li et al. 2009). Similarly, "alternariol" produced by endophytic *Alternaria brassicicola* ML-PO8 exhibited a comparable xanthine oxidase inhibitory activity with an IC_{50} value of 15.5 μM (Gu 2009). Two non-purine XOI were isolated from the culture filtrate of endophytic *Lasiodiplodia pseudotheobromae* and *Muscodor darjeelingensis respectively*. The IC_{50} values of XOI from the two endophytes were 0.61 and 0.54 μg/ml, respectively, which were much lower than allopurinol but were higher than that of febuxostat under in vitro conditions. Furthermore, both the isolates showed 84–88% reduction in the uric acid production which is comparable with the commercially available drugs under laboratory conditions (Kapoor and Saxena 2014, 2016). Recently, silver nanoparticles synthesized from the extract of endophytic *Penicillium* sp. also displayed the ability to strongly inhibit xanthine oxidase (IC_{50}: 92.65± 1.81 μg/mL). Further, the fungus also showed strong antibacterial, antioxidant, and antilipoxygenase activity (Govindappa et al. 2016). The published reports suggest that endophytes can be taken into account for the development of novel XOI.

4.3.6 Quorum Sensing Inhibitors

Quorum sensing is a process of communication between the bacterial cells that involves the production, detection, and response to an extracellular signaling molecule known as autoinducers. These autoinducers increase in concentration as a function of cell density (Rutherford and Bassler 2012). At low cell densities, bacteria behave as unicellular organisms; however they shift their behavior to multicellular type following stimuli that their cell densities have reached a threshold level (Kalia 2013). The intensity of communication signal reflects the population of bacterial cells in a particular environment, and hence the level of signal ensures that density of bacterial cells is enough to make behavioral changes which are termed as "quorate" (Hentzer and Givskov 2003). This mechanism enables bacteria to overpower human defense system and cause various diseases. To control the virulence of particular pathogenic bacterial species, these communication channels between the bacterial cells need to be ceased. Quorum sensing inhibitors showed promising effect as an alternative to antibiotics, and this is the reason why several have been largely studied from synthetic and natural resources (Defoirdt et al. 2013).

Quorum sensing mechanism can be measured by studying the ability to suppress violacein production by the sensor stain *Chromobacterium violaceum* (Rajesh and Rai 2014). Ma et al. (2013) screened over 1100 endophytic isolates isolated from tobacco leaf for their quorum sensing inhibitory activity. Out of 1177, only 168 isolates showed strong quorum quenching ability. Among them, *Lysinibacillus fusiformis*, *Pseudomonas geniculata*, *Serratia marcescens*, and *Bacillus cereus* showed maximum lactonase activity. Further, the culture filtrates of two endophytic bacteria *Bacillus firmus* PT18 and *Enterobacter asburiae* PT39 exhibited strong quorum sensing inhibition by reducing violacein production by 80%. These culture filtrates also showed strong inhibition of biofilm in *Pseudomonas aeruginosa* (Rajesh and Rai 2014). Similarly, endophytic *Bacillus megaterium* and *Brevibacillus borstelensis* and two *Bacillus* sp. isolated from *Cannabis sativa* also showed quorum sensing inhibition by reducing violacein production (Kusari et al. 2014). Bacterial endophytes *Microbacterium testaceum* BAC1065, BAC1100, and BAC2153, *Bacillus thuringiensis* BAC3151, and *Rhodococcus erythropolis* BAC2162 also exhibited quorum quenching activity against *Pseudomonas syringae* and *Hafnia alvei* (Lopes et al. 2015). Recently, culture filtrate of endophytic bacterium *Bacillus cereus* displayed strong quorum sensing inhibitory activity against *Pseudomonas aeruginosa* and *Pectobacterium carotovorum* (Rajesh and Rai 2016).

Fungal endophytes such as *Fusarium graminearum* and *Lasiodiplodia* sp. showed decreased production of violacein which suggested antiquorum activity (Rajesh and Rai 2013). Similarly, the biomass and cell-free extract of marine endophytes *Sarocladium* sp. (LAEE06), *Fusarium* sp. (LAEE13), *Epicoccum* sp. (LAEE14), and *Khuskia* sp. (LAEE 21) strongly suppressed violacein production by 70% (Martin-Rodriguez et al. 2014). Further, polyhydroxyanthraquinones produced by *Penicillium restrictum* act as a quorum sensing inhibitor against the spectrum of methicillin-resistant *Staphylococcus aureus* with an IC_{50} value of 8–120 μM

(Table 4.2) (Figueroa et al. 2014). Thus, quorum sensing inhibitors from endophytes can be a useful agent in both biocontrol and clinical arena.

4.3.7 Urease Inhibitors

Urease is an enzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide. The enzyme accelerates the reaction by 100 trillion-fold as compared to nonenzymatic reaction. Ureases are important virulence factor in the gastrointestinal and urinary tract infections caused by *Helicobacter pylori* or various *Proteus* species. Infections caused by ureolytic bacteria lead to serious health problems like pyelonephritis, hepatic coma, peptic ulcer, and kidney stones (Upadhyay 2012; Modolo et al. 2015; Khan et al. 2015). Urease inhibitors are molecules that suppress the hydrolytic action of urease. Urease inhibitors are found to dissolve kidney stone and also prevent the formation of new crystals in urine. They are also considered as potential targets of antiulcer drug. Until now, only one compound, acetohydroxamic acid has been clinically approved for treatment of urinary tract infection in which the patient also suffers from several side effects. Thus, there is a requirement for development of novel, selective, and efficient urease inhibitors which could assure the requirements of low toxicity and cost-effectiveness (Kosikowska and Berlicki 2011; Macegoniuk 2013).

The study carried out by Haroon et al. (2014) demonstrated that the ethyl acetate extracts of marine-derived endophytic fungus *Aspergillus terreus* exhibited potential urease inhibitory activity with an IC_{50} value of 116.8 μM. Further, a new radicinol derivative, bipolarisenol, isolated from the ethyl acetate extract of endophytic fungus *Bipolaris sorokiniana* LK12 also showed promising urease inhibition in a dose-dependent way with an IC_{50} value of 81.62 μg/ml. The compound also possessed acetyl cholinesterase and lipid peroxidation inhibitory properties (Table 4.2, Fig. 4.1) (Khan et al. 2015). Similarly, sorokiniol isolated from the same fungus also displayed 50% urease inhibition (Ali et al. 2016). Recently, fungal endophytes isolated from *Boswellia sacra* also exhibited urease inhibition. Isolate *Fusarium oxysporum* FEF1, *Penicillium spinulosum* FEF2, *Aspergillus caespitosus* FEF3, *Alternaria alternata* FEF5, and *Penicillium citrinum* FEF6 showed 45–85% inhibitory activity on urease. Further, the organic extract of *Penicillium citrinum* FEF6 was fractionized into five different compounds which showed moderate urease inhibitory activity (20–40%) which clearly depicted that the isolate possessed synergistic inhibitory activity (Ali et al. 2017). The present reports are scanty and preliminary, and it requires extensive research for the development of new urease inhibitors from endophytic microorganisms.

4.3.8 Protease Inhibitors

Protease inhibitors (PIs) are lead molecules that block the activity of protein-digesting enzymes, "proteases," involved in viral replication and pathogenesis. PIs

check viral replication by selectively binding to viral proteases, thereby blocking the hydrolytic cleavage of precursor proteins, essential for production of pathogenesis (Ghosh et al. 2016). Thus, PIs play a significant role in the treatment of viral diseases including human immunodeficiency virus (HIV), herpesvirus, and hepatitis C virus (HCV). Although several PIs like saquinavir, nelfinavir, ritonavir, and atazanavir are already available for clinical use, emergence of toxicity, new recombinant viral strains, and drug resistance have daunting effect on current antiviral therapy. Thus, development of new antiviral drugs is the need of the hour to deal with the present scenario (Singh et al. 2004; Roy 2017).

Natural products have always been the mainstay of structurally diverse bioactive secondary metabolites. Several potential antiviral compounds have been reported from endophytic fungi. Two *p*-tridepside derivatives, cytonic acids A and B, isolated from endophytic *Cytonaema* sp. exhibited human cytomegalovirus protease inhibitory activity with an IC_{50} values of 43 and 11 μmol, respectively (Table 4.2, Fig. 4.1; Guo et al. 2000). Singh et al. (2004) reported the production of hinnuliquinone, a potential inhibitor of HIV-1 protease from endophytic fungi inhabiting leaves of oak tree. The compound showed strong inhibition of protease isolated from drug-resistant wild-type mutant strain of HIV (A-44) with an IC_{50} values of 2.5 and 1.8 μM, respectively. (+)-Sclerotiorin isolated from the hexane extract of endophytic *Penicillium sclerotiorum* PSU-A13 also displayed inhibitory effect on the HIV-1 protease with an IC_{50} of 62.7 μg/mL (Arunpanichlert et al. 2010). Further, pestalotheols A–D isolated from endophytic *Pestalotiopsis theae* were also tested for their inhibitory activity of HIV-1 replication. It was observed that among the four metabolites, pestalotheol C exhibited inhibitory effect on HIV-1 replication in C8166 cells with an IC_{50} value of 16.1 μM (Li et al. 2008). Similarly, altertoxins (V, I, II, and III) isolated from endophytic *Alternaria tenuissima* QUE1Se completely inhibited replication of HIV-1 virus (Bashyal et al. 2014). Govindappa et al. (2015) reported that the organic extract of *Alternaria* sp., *Fusarium* sp., and *Trichoderma harzianum* inhibited the activity of HIV reverse transcriptase, integrase, and protease enzymes, respectively.

Anthraquinones isolated from endophytic marine fungus *Aspergillus versicolor* showed inhibition of HCV protease. The ethyl acetate extract along with isorhodoptilometrin-1-methyl ether, emodin, 8-methyl-emodin, siderin, arugosin C, and variculanol inhibited hepatitis C virus NS3 protease (Hawas et al. 2012). Similarly, alternariol derivatives obtained from the extract of *Alternaria alternata* displayed high-level inhibition of HCV. The ethyl acetate extract, alternariol, and maculosin depicted strong inhibition of HCV NS3/4A protease with IC_{50} values of 14, 32.2, and 12 μg/ml, respectively (Hawas et al. 2015). Recently, endophytic *Penicillium chrysogenum* isolated from red alga *Liagora viscida* also showed potential inhibitory activity toward HCV NS3/4A protease with an IC_{50} value of 20 μg/mL (Hawas et al. 2013). Further, the culture metabolites obtained from marine endophytic *Fusarium* sp. were capable of inhibiting hepatitis C virus NS3/4A protease. Among the tested compounds, ω-hydroxyemodin and griseoxanthone C showed maximum inhibition with IC_{50} values of 10.7 and 19.8 μM, respectively (Hawas et al. 2016). Thus, endophytes appear to be a promising source of novel

antiviral metabolites. However, the number of antiviral compounds reported to date is very handful, and there is a need to search for newer biotypes from different ecological niches, which could produce novel lead molecules with potential antiviral activity.

4.3.9 DNA Polymerase Inhibitors

DNA polymerases are enzymes that synthesize DNA. Human genome encodes for about 16 types of polymerases that are involved in highly regulated functions like DNA synthesis, repair, and recombination. Eukaryotic cell comprises of 3 replicative polymerases (α, δ, and ε), a mitochondrial polymerase (γ), and 11 non-replicative polymerases (β, ξ, η, θ, ι, κ, λ, μ, ν, terminal deoxynucleotidyl transferase, and REV1). Based on their sequence similarity, eukaryotic polymerases are classified into four families A, B, X, and Y. Family A contains mitochondrial polymerase γ and non-replicative polymerases θ and ν, whereas family B includes three replicative polymerases (α, δ, and ε) and non-replicative polymerase ξ. Family X comprises of non-replicative polymerases β, λ, and μ and terminal deoxynucleotidyl transferase, whereas family Y contains polymerases η, ι, κ, and REV1 (Kamisuki et al. 2007; Kimura et al. 2008; Nishida et al. 2008).

Numerous pathological conditions like cancer, autoimmune disorders, and bacterial or viral infections are often caused due to uncontrolled DNA replication. Inhibition of this vital biological process provides an obvious management strategy against these diseases (Berdis 2008). Solanapyrone A, isolated from fungus SUT 01B1-2, selectively inhibits DNA polymerases β and λ with an IC_{50} values of 30 and 37 μM, respectively (Table 4.2, Fig. 4.1) (Mizushina et al. 2001). Similarly, kasanosins A and B isolated from the culture filtrates of marine-derived *Talaromyces* sp. also inhibited β and λ DNA polymerases in a dose-dependent way. Kasanosins A showed comparatively strong inhibition of rat polymerase β and human polymerase λ with IC_{50} values of 27.3 and 35 μM, respectively (Kimura et al. 2008). Hymenoic acid produced by the coral-derived fungus *Hymenochaetaceae* sp. exclusively inhibited λ DNA polymerase with an IC_{50} value of 91.7 μM in a noncompetitive manner (Nishida et al. 2008). Further, trichoderonic acids A and B and (+)-heptelidic acid isolated from *Trichoderma virens* IG34HB competitively suppressed the activity of mammalian non-replicative DNA polymerases β, λ, and terminal deoxynucleotidyl transferase (Yamaguchi et al. 2010).

1-deoxyrubralactone isolated by the fungal strain HJ33 derived from sea algae selectively inhibited X and Y families of eukaryotic DNA polymerase with an IC_{50} values of 11.9–59.8 μM, respectively (Naganum et al. 2008). Further, *Penicillium daleae* isolated from sea moss produced Penicilliols A and B which exclusively inhibited Y family of mammalian DNA polymerase with IC_{50} values of 19.8–32.5 μM, respectively (kimura et al. 2009). Another *Penicillium* sp. from seaweed produced pinophilins A and B which potentially inhibited A, B, and Y families of DNA polymerase. Pinophilins A exhibited strongest inhibition in a noncompetitive manner with IC_{50} values of 48.6–55.6 μM. Thus, selective polymerase inhibitors are

considered as a feasible candidate in chemotherapy because many of them can inhibit human cancer cell proliferation and were also found to be cytotoxic (Myobatake et al. 2012).

4.3.10 Trypanothione Reductase Inhibitor

Protozoan parasites like *Trypanosoma* and *Leishmania* found at the tropical and subtropical regions of the world affect millions of people resulting in massive medical, economic, and social loss in the affected area (Beig et al. 2015; Campos et al. 2015; Fatima et al. 2016a, b). The World Health Organization (WHO) has listed all the diseases caused by these parasites among neglected tropical disease. The current arsenal of drugs available in the market for the treatment of different forms of leishmaniasis and trypanosomiasis were introduced several decades ago and has significant drawbacks like efficacy, toxicity, drug resistance, and cost-effectiveness. Hence, there is an utmost requirement of finding out new drugs with better efficacy and lower toxicity (Campos et al. 2008; Cota et al. 2008). Trypanothione reductase is an enzyme found in several trypanosomatids including *Leishmania* and *Trypanosoma* spp. Trypanothione reductase is involved in the protection of *Trypanosoma* and *Leishmania* sp. against oxidative stress and is considered as a potential drug target for treatment against trypanosomatids (Garrard et al. 2000; Beig et al. 2015).

Alentusin, a biphenyl derivative isolated from the organic extract of endophytic fungus *Alternaria* sp. UFMGCB55 significantly inhibited 99% of trypanothione reductase with an IC_{50} value of 4.3 μM (Table 4.2, Fig. 4.1) (Cota et al. 2008). Organic extract of endophytic *Cochliobolus* sp. exhibited 90% inhibition of *Leishmania amazonensis* and 100% reduction of Ellman's reagent in trypanothione reductase assay under in vitro conditions. Further, the fractionation of the extract eluted two compounds, cochlioquinone A and isocochlioquinone A, both of which were active against *L. amazonensis* with an EC_{50} value of 1.7 and 4.1 μM, respectively (Campos et al. 2008). Rosa et al. (2010) screened 121 isolates obtained from various Brazilian forests for leishmanicidal and trypanocidal activity. The ethyl acetate extract of 11 isolates inhibited *L. amazonensis* with an IC_{50} values ranging from 4.6 to 24.4 μg/ml. Endophytic isolate UFMCB 529 and 910 exhibited 90% inhibition in the growth of *L. amazonensis.* Further, 24 isolates displayed inhibition of trypanothione reductase, while only 3 of them showed inhibitory effect (>60%) on the growth of *Trypanosoma cruzi* with an IC_{50} values of 1–10 μg/ml. Extract of endophytic isolates UFMCB 508, 509, 513, 529, 563, 579, and 648 inhibited trypanothione reductase and was also active against the amastigote forms of *L. amazonensis*. Isolate UFMCB 508 displayed comparable activity with benznidazole, an antiparasitic medication used in Chagas disease (Rosa et al. 2010). Furthermore, over 560 endophytic isolates recovered from Antarctic angiosperms *Deschampsia antarctica* were also screened for their leishmanicidal activity. Extract of 12 isolates checked the proliferation of *L. amazonensis* with IC_{50} values ranging from 0.2 to 125 μg/ml. Further, *Alternaria*, *Cadophora*, *Herpotrichia*, and *Phaeosphaeria* spp.

showed >90% killing of *L. amazonensis*. It will be interesting to examine whether extracts derived from endophytic isolates possess leishmanicidal activity via trypanothione reductase inhibition or not (Santiago et al. 2012). Recently, Fatima et al. (2016a, b) used in silico approach to study antileishmanial activity of epicoccamide derivatives A–D (endophytic origin). The study revealed that epicoccamide derivatives were stabilized at the active site of the enzyme via hydrogen bond and hydrophobic interactions. Epicoccamide derivatives depicted high binding energies with trypanothione reductase with binding energies of -13.31, -13.44, -13.31, and -13.32 Kcal/mol, respectively. Thus, trypanothione reductase inhibitors from endophytic isolates could serve as novel lead molecules in the management of neglected tropical diseases like trypanosomiasis and leishmaniasis.

4.3.11 DNA Topoisomerase Inhibitors

DNA topoisomerases are crucial enzymes that play a significant role in DNA replication and cell division. They are involved in uncoiling and recoiling of DNA. Based on their catalytic mode of action, they are classified into two different types: topoisomerase I and topoisomerase II. Topoisomerase I relaxes DNA supercoiling during replication and transcription by transiently creating a single-strand nick in the DNA, whereas topoisomerase II acts by making a transient double-strand breaks in DNA. Topoisomerase is recognized as target for anticancer drugs (Pommier 2009; Jarolim et al. 2017). The inhibitors block the activity of topoisomerase to bind the DNA back together after it has been cut, making the enzyme nonfunctional. Topoisomerase inhibitors have the ability to kill cells undergoing DNA replication, stop translation of DNA for protein production, and prevent DNA damage and repair. Since, cancer cell proliferates more rapidly than the normal cells, and the cancer cells will be disproportionately killed by the topoisomerase inhibitors. Topoisomerase inhibitor I includes camptothecin, whereas topoisomerase inhibitor II comprises of doxorubicin and etoposides which have displayed remarkable therapeutic potential against certain cancers including breast, bladder, colon, uterine, cervical, and ovarian cancer (Kusari et al. 2009a; Baikar and Malpathak 2010). Camptothecin and its derivatives are the third largest anticancer drugs. Both camptothecin and podophyllotoxin (precursor of etoposides) are plant products originally isolated from the *Camptotheca acuminata* and *Podophyllum* sp., respectively. The huge market demand caused large-scale destruction of source plants from their natural environment resulting into endangered species status of the plants. Further, toxicity, short half-life, and cellular uptake were some important shortcomings related to them. Hence, alternative sources need to be exploited to meet the global market demand with effective therapeutic potential (Puri et al. 2006; Pu et al. 2013).

Endophytes have been reported as prolific producers of anticancer agents. The discovery of billion-dollar anticancer drug paclitaxel from *Taxomyces andreanae*, an endophyte of *Taxus brevifolia*, was a breakthrough discovery in endophytic research (Stierle et al. 1993). Since then, many anticancer agents have been isolated from various endophytic fungi. Puri et al. (2005) first reported the production of

camptothecin from endophytic *Entrophospora infrequens* obtained from *Nothapodytes foetida*. Further, Kusari et al. (2009a) isolated a camptothecin and its derivatives producing endophytic fungus *Fusarium solani* from *Camptotheca acuminata*. Furthermore, camptothecin-producing endophytic *Aspergillus* sp. LY341, *Aspergillus* sp. LY355, and *Trichoderma atroviride* LY357 were also isolated from *Camptotheca acuminata* collected from campus of the Chengdu Institute of Biology of the Chinese Academy of Sciences, Chengdu, China (Pu et al. 2013). Similarly, Shweta et al. (2010) also documented the production of camptothecin, hydroxycamptothecin, and 9-methoxycamptothecin from endophytic *Fusarium solani* isolated from *Apodytes dimidiata*. Apart from endophytic fungi, camptothecin and its derivative 9-methoxy camptothecin production were also observed in endophytic bacteria isolated from *Miquelia dentata* (Shweta et al. 2013).

Podophyllotoxin is the precursor for chemical synthesis of anticancer drugs like etoposide and teniposide (topoisomerase II inhibitors) that are used in breast, lung, and testicular cancer therapy. Yang et al. (2003) first reported the production of podophyllotoxin from six endophytic fungi isolated from *Sinopodophyllum hexandrum*, *Diphylleia sinensis*, and *Dysosma veitchii*. Later, Eyberger et al. (2006) isolated two strains of endophytic *Phialocephala fortinii* PPE5 and *Phialocephala fortinii* PPE7 that possessed the ability to produce podophyllotoxin. Similarly, podophyllotoxin and its glycoside production were also detected in the Sabouraud broth culture of endophytic *Trametes hirsute* isolated from *Sinopodophyllum hexandrum* (Puri et al. 2006). Furthermore, endophytic *Fusarium oxysporum* and *Aspergillus fumigates* isolated from *Juniperus communis* also exhibited production of podophyllotoxin (Kour et al. 2008; Kusari et al. 2009b). The above reports suggest that endophytes could be a promising natural resource for obtaining camptothecin, podophyllotoxin, and their derivatives.

Apart from producing anticancer molecules like camptothecin and podophyllotoxin, endophytes are also documented to exhibit inhibition of topoisomerase enzymes. Guo et al. (2007) first reported the inhibition of topoisomerase I by secalonic D produced from endophytic *Paecilomyces* species. Similarly, Xiaoling et al. (2010) screened ethyl acetate extract of 56 endophytic fungi isolated from mangrove plants in Qi'ao island of Zhuhai, China, among which extract of 19 fungal isolates showed topoisomerase I inhibitory activity. Further, Shino et al. (2007) reported production of fusaristatins B, a new cyclic lipopeptides from an endophytic *Fusarium* sp. that appreciably inhibited topoisomerase I and II with an IC_{50} values of 73 μM and 98 μM, respectively (Table 4.2, Fig. 4.1). Similarly, aspergiloid I, produced by endophytic *Aspergillus* sp. YXf3, possessed the ability to inhibit topoisomerase II (Guo et al. 2014). Thus, from the above reports, it clearly becomes evident that endophytes are promising alternative source of topoisomerase inhibitors which can be developed as a potential anticancer agents.

4.3.12 Aromatase Inhibitor

Breast cancer is one of the foremost causes of mortality in women around the world. Every one in eight women in America is expected to be diagnosed with breast cancer in her lifetime. Tumor cell proliferation is stimulated by the circulating estrogen; that is why over 75% of the patients diagnosed with breast cancer have estrogen-dependent breast cancer. In breast cancer tissues, an increased level of enzyme aromatase was found around the tumor site (Chomcheon et al. 2009; Fatima et al. 2014). Aromatase is an enzyme that carries out the catalytic conversion of androgens into estrogens. Thus by ceasing the activity of the aromatase enzyme, 90% of the estrogen production can be reduced which will significantly reduce the chances of breast cancer. Presently, aromatase inhibitors like letrozole and exemestane are used as hormonal therapy in patients with estrogen-dependent postmenopausal breast cancer (Altundag and Ibrahim 2006; Sureram et al. 2012; Chottanapund et al. 2017). Thus, aromatase inhibitors appear to be a plausible target for treatment of estrogen-dependent breast cancer, and new avenues need to be explored for finding out novel aromatase inhibitors.

Corynesidone A isolated from the broth extract of endophytic fungus *Corynespora cassiicola* exhibited aromatase inhibitory activity with an IC_{50} value of 5.3 μM (Table 4.2, Fig. 4.1). The compound also showed strong antioxidant activity (Chomcheon et al. 2009). Similarly, isocoumarins and phthalide extracted from the culture filtrate of the endophytic fungus *Colletotrichum* sp. CRI535-02 were also capable of inhibiting aromatase enzyme with an IC_{50} ranging from 15.3 to 16.9 μM (Tianpanich et al. 2011). Further, azaphilone derivative derived from the endophytic fungus *Dothideomycetes* sp. CRI7 also showed aromatase inhibitory activity with an IC_{50} value of 12.3 μM (Hewage et al. 2014). Recently, two endophytic isolates *Epicoccum nigrum* and *Penicillium* sp. isolated from west Himalayan yew *Taxus fuana* exhibited 73–76% aromatase inhibition with IC_{50} values of 12.2 and 10.5 μg/ml, respectively (Fatima et al. 2016a, b).

Depsidones produced by a marine-derived fungus *Aspergillus unguis* CRI282-03 were capable of inhibiting aromatase enzyme with IC_{50} values of 1.2–11.2 μM, respectively (Sureram et al. 2012). Further, two despidones, unguinol and aspergillusidone A, were also tested for their antiaromatase activity against human primary breast adipose fibroblasts and hormonal-responsive T47D breast tumor cells. It was found that despidones inhibited the growth of T47D breast tumor cells via inhibition of aromatase activity with an IC_{50} of 9.7 and 7.3 μM, respectively (Chottanapund et al. 2017). Thus, endophytic fungi appear to be a unique natural bioresource of aromatase inhibitors with huge possibilities in breast cancer therapy.

4.3.13 α-Amylase and α-Glucosidase Inhibitors

Diabetes mellitus (DM) is a serious global health problem characterized by chronic hyperglycemia and disturbed carbohydrate, fat, and protein metabolism (Indrianingsiha and Tachibana 2017; Ruzieva et al. 2017). DM is linked with other

complications like cardiovascular disorders, retinopathy, nephropathy, and neuropathy (El-Hady et al. 2014). The number of people suffering from DM is alarming, and it is believed that about 522 million peoples will be affected by the year 2030. India is expected to have maximum number of diabetes patients in the coming years (Akshatha et al. 2014; Pavithra et al. 2014; Singh and Kaur 2015). Type 2 diabetes is the most prevalent type of diabetes, with >90% of people suffering from it. Postprandial hyperglycemia is a major risk factor involved in type 2 diabetes. The elevated level of postprandial hyperglycemia is attributed to the action of two carbohydrate-hydrolyzing enzymes, viz., α-amylase and α-glucosidase. The enzymes are involved in breakdown complex sugar moieties into more simpler and absorbable form, leading to increased blood sugar level. One of the management strategies of DM involves inhibition of these enzymes. Inhibition of these enzymes slows down the rate of carbohydrate digestion and glucose absorption, ultimately lowering hyperglycemia. Thus, inhibition of α-glucosidase and α-amylase appears to be an effective target for diabetes management (Pujiyanto et al. 2012; Xia et al. 2015; Ruzieva et al. 2017). The oral antidiabetic drugs like acarbose and miglitol are inhibitors of α-glucosidase. However, these agents are synthetic in origin and suffer from various adverse effects like flatulence, abdominal pain, renal tumors, hepatic injury, etc. (Pavithra et al. 2014). These synthetic drugs need to be replaced with drugs of natural origin that are believed to have lesser or no side effects.

The recent studies suggested that endophytic microorganisms offer themselves as magnificent producers of α-glucosidase and α-amylase inhibitors. Endophytic actinomycetes isolated from various Indonesian diabetic plant species exhibited α-glucosidase inhibitory activity. Among the screened actinomycetes, *Streptomyces olivochromogenes* BWA65 obtained from *Tinospora crispa* displayed maximum α-glucosidase inhibition (Pujiyanto et al. 2012). Similarly, Akshatha et al. (2014) reported that extract of *Streptomyces longisporoflavus* competently inhibited α-amylase with an IC_{50} value of 162 μg/mL.

Several marine-derived fungi were also reported to possess antidiabetic property. Eremophilane sesquiterpenes isolated from endophytic *Xylaria* sp. inhibited α-glucosidase with an IC_{50} value of 6.54 μM (Song et al. 2012). The mycelial and culture filtrate extract of a coral-derived fungus *Emericella unguis* 8429 also displayed 51 and 64% inhibition of α-glucosidase enzyme (El-Hady et al. 2014). Similarly, isopimarane diterpene and 11-deoxydiaporthein A produced from *Epicoccum* sp. HS-1 also demonstrated α-glucosidase inhibitory activity with IC_{50} values of 4.6 and 11.9 μM, respectively (Xia et al. 2015).

Endophytic fungi from terrestrial plants are considered as lucrative source of antidiabetic agents. Ramdanis et al. (2012) screened endophytic fungi isolated from the seeds of *Swietenia macrophylla* for α-glucosidase inhibitors. During the study, five isolates showed α-glucosidase inhibitory activity. The IC_{50} value of most potent isolate CMM4B (73.64 μg/ml) was found to be better than that of acarbose (117.06 μg/ml) under in vitro conditions. Similarly, endophytic *Colletotrichum* sp. isolated from *Taxus sumatrana* showed 71% inhibition of α-glucosidase (Artanti et al. 2012). Thielavins A, J, and K isolated from endophytic fungal isolate MEXU 27095 inhibited α-glucosidase in a dose-dependent way with IC_{50} values of 23.8, 15.8, and

22.1μM, respectively (Rivera-Chavez et al. 2013). Recently, Indrianingsiha and Tachibana (2017) reported production of a potential α-glucosidase inhibitor from Xylariaceae sp.QGS01. Similarly, Ali et al. (2017) also determined α-glucosidase inhibitory activity of an endophytic *Penicillium citrinum* isolated from *Boswellia sacra*. Furthermore, Pavithra et al. (2014) screened extract of 22 endophytic fungal isolates obtained from *Momordica charantia* and *Trigonella foenum-graceum* for α-amylase, α-glucosidase, and aldose reductase inhibitory activity. Isolate *Stemphylium globuliferum* PTFL005 and PTFL011 displayed α-glucosidase inhibitory activity with IC_{50} values of 17.37 and 10.71 μg/mL, whereas isolate *Stemphylium globuliferum* PTFL005 and PTFL006 showed promising α-amylase inhibitory activity with an IC_{50} values of 15.48 and 13.48 μg/ml, respectively. Further, *Trichoderma atroviride* PMCF003 displayed moderate aldose reductase inhibitory property. Recently, fungal endophytes isolated from the medicinal diabetic plants of Uzbekistan were also screened for their α-amylase inhibitory activity. The screened isolates showed 60–82% inhibition of α-amylase (Ruzieva et al. 2017). Peptides produced by endophytic *Aspergillus awamori* exhibited both α-amylase and α-glucosidase inhibitory activity with low IC_{50} values of 3.75 and 5.62 μg/mL, respectively. The inhibitor was stable over a range of high and low pH and temperature and was non-mutagenic in nature (Singh and Kaur 2015). The above reports suggest that endophytes can be harnessed as new α-amylase and α-glucosidase inhibitors for the better management of diabetes.

4.3.14 Pancreatic Lipase Inhibitors

Obesity is a burgeoning health concern which occurs due to an imbalance between calorie uptake and utilization. Today, obesity is becoming the major cause of preventable deaths, both in developed and developing nations. It has been reported that every third individual around the globe is obese. Further, it has also been projected that if the current scenario continues, by the end of year 2020, every two individuals out of three will be overweight or obese (Fitri et al. 2017; Katoch et al. 2017). The management of obesity can be done by two different anti-obesity therapies including exercise and/or drug therapy. Drug therapy is more convincing as there is relapse of weight gain after physical activity has been stopped. Drug therapy includes targeting drugs to central or peripheral nervous system eventually leading to loss of hunger and lipase inhibition (Lunagariya et al. 2014). Pancreatic lipase (PL) is the key enzyme involved in lipid metabolism. PL hydrolyzes about 50–70% of the triglycerides resulting in the formation of monomers of fatty acids that are absorbed and accumulated in the body resulting to obesity (Gupta et al. 2014; Sharma et al. 2017). Hence, PL appears to be suitable target for obesity management. Orlistat isolated from actinobacterium *Streptomyces toxytricini* is one of the best-selling (PL inhibitor) anti-obesity drug. However, it also suffers from several side effects like oily stools, flatulence, fecal urgency, and abdominal cramps. Thus, alternative avenues need to be explored for isolation of novel PL inhibitors with low or no side effects (Gupta et al. 2015).

Natural products either from plants or microorganisms offer themselves as potential source of PL inhibitor. Many natural products have been reported to exhibit inhibition of PL. However, very preliminary reports are available on PL inhibitors from endophytic microorganisms. Gupta et al. (2014) first reported PL inhibitors from endophytic fungi. A screening program was designed to screen endophytic fungi from *Aegle marmelos* collected from biodiversity hot spots of India. Among the screened fungi, endophytic *Fusarium incarnatum* (#6AMLWLS), *Botryosphaeria stevensii* (#59 AMSTWLS), and *Fusarium semitectum* (#1058 AMSTITYEL) showed maximum inhibition of PL. Further, the IC_{50} value of aqueous extract of *F. incarnatum* was 2.12 μg/ml which was better than commercially available drug orlistat (2.79 μg/ml) under in vitro conditions. The lead molecule was further purified and characterized using analytical and biochemical tools and was identified as a novel tetrapeptide "Fustat" (patent filing under process) (Table 4.2). Similarly, culture filtrates obtained from endophytic fungi isolated from medicinal plants like *Cinnamomum camphora*, *C. zeylanicum*, *Camellia sinensis*, *Piper nigrum*, and *Taxus baccata* were also screened for PL inhibitory activity. The chromogenic plate assays indicated that endophytic fungal isolate #57 TBBALM (*Penicillium* sp.), #33 TBBALM (*Mycelia sterilia*), and #1 CSSTOT (*Schizophyllum* sp.) exhibited maximum inhibition of PL. Further, the IC_{50} value of organic extract of #57 TBBALM (3.69 μg/ml) was also found to be comparable with orlistat (2.73 μg/ml) (Gupta et al. 2015). Recently, Katoch et al. (2017) reported inhibition of PL by the crude extracts of endophytic fungi obtained from *Viola odorata*. Among the tested fungi, ten isolates showed potential inhibition of PL with IC_{50} value >1 μg/ml. *Aspergillus* sp. VOLF4 exhibited promising PL inhibition with an IC_{50} value of 3.8 μg/ml. Apart from endophytic fungi, PL inhibitory activity of endophytic actinobacteria has also been recently reported. Endophytic *Streptomyces* isolates AEBg4, AEBg10, AEBg12, AELk3, and AEKp9 isolated from various Indonesian medical plants showed significant inhibition (92–96%) of PL (Fitri et al. 2017). The above reports suggest that endophytic isolates are promising source of PL inhibitors. However a more detailed, rationalized, and target-based studies are required before moving to preclinical trials.

4.4 Conclusion

Endophytes are considered as a rich source of structurally diverse bioactive metabolites having potential application in agriculture, pharmaceutical, and food industry. However, looking at the humongous biodiversity of endophytic microorganisms, it seems that they still remain an underexplored resource of enzyme inhibitors. The published reports are scanty, and issues like low productivity, toxicity, cellular uptake, and short half-life need to be resolved first. The advances made in the field of modern biotechnology such as genetic engineering and microbial fermentation technology should be taken into consideration for better understanding and successive manipulation of endophytic microorganism and to make it more beneficial for the mankind. The first step toward this approach is exploration of a potential

candidate from the natural environment. Further, through fusion, mutation, recombination, and genetic manipulations, the viable candidate should be selected for large-scale fermentation. The strategy promises to improve the production of therapeutically important enzyme inhibitors at cheaper and more affordable cost. Apart from this, there is a need among different scientific disciplines (microbiologist, chemist, toxicologist, and pharmacologist) to work in a coordinated manner for the discovery of the target lead molecule. If we will be able to achieve the above mentioned targets, enzyme inhibitors from endophytic microorganisms will emerge as a future medicine which can be used to cure all major health problems.

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