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Exploring the potential of endophytes from medicinal plants as sources of antimycobacterial compounds

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ABSTRACT

Natural product drug discovery has regained interest due to low production costs, structural diversity, and multiple uses of active compounds to treat various diseases. Attention has been directed towards medicinal plants as these plants have been traditionally used for generations to treat symptoms of numerous diseases.

It is established that plants harbour microorganisms, collectively known as endophytes. Exploring the as-yet untapped natural products from the endophytes increases the chances of finding novel compounds. The concept of natural products targeting microbial pathogens has been applied to isolate novel antimycobacterial compounds, and the rapid development of drug-resistant *Mycobacterium tuberculosis* has significantly increased the need for new treatments against this pathogen. It remains important to continuously screen for novel compounds from natural sources, particularly from rarely encountered microorganisms, such as the endophytes.

This review focuses on bioprospecting for polyketides and small peptides exhibiting antituberculosis activity, although current treatments against tuberculosis are described. It is established that natural products from these structure classes are often biosynthesised by microorganisms. Therefore it is hypothesised that some bioactive polyketides and peptides originally isolated from plants are in fact produced by their endophytes. This is of interest for further endophyte natural product investigations.

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1. Natural product drug discovery

The need for novel chemical compounds to treat human diseases is ever increasing. The rapid development of drug-resistant microbes, the discovery of new cases of life-threatening infections, and the constant recurrence of diseases have pushed for advances in the field of drug discovery (Strobel et al., 2004; Demain, 2000). In principle, there are three pathways for discovering new pharmacologically significant compounds: rational drug design, where the drug is purposefully tailored towards specific targets in the microbial cell (Mandal et al., 2009); combinatorial chemistry, which involves synthesis of a combinatorial library of compounds, which are then tested against the cellular target to determine the most potent compounds (Gallop et al., 1994); and natural product discovery, by isolating bioactive compounds from biological sources (Strohl, 2000). Of late, pharmaceutical companies have shifted their interest towards the first two pathways. These pathways utilise the latest advances in three-dimensional X-ray crystallography, drug-docking tools, and other computer-aided methodologies (Müller, 2009) which significantly cut the development time of a compound, from compound synthesis to market delivery. There are, however, downfalls with these approaches, including the high cost to discover novel compounds and for production. Moreover, until the detailed mechanisms of targeted cellular death and survival are comprehensively elucidated, it will remain difficult to select potential targets for structure-guided drug design (Barry and Blanchard, 2010). Furthermore, being laboratory-synthesised compounds, combinatorial compounds are often insufficiently complex, possessing limited structural rigidity, and require extensive purification steps and bioactivity testing to conclusively characterise the bioactive compounds (Baker et al., 2000). In addition, there has been a steady increase in the negative public perception regarding the use of synthetic drugs due to their long-term safety and environmental concerns (Strobel and Daisy, 2003). Consequently, efforts are being made to re-explore the potential of natural products as sources of novel drugs (Fig. 1).

2. The ethnobotanical approach to drug discovery

Natural products, generally secondary metabolites, are produced by an organism in response to external stimuli such as nutritional changes or foreign infection (Strohl, 2000). They

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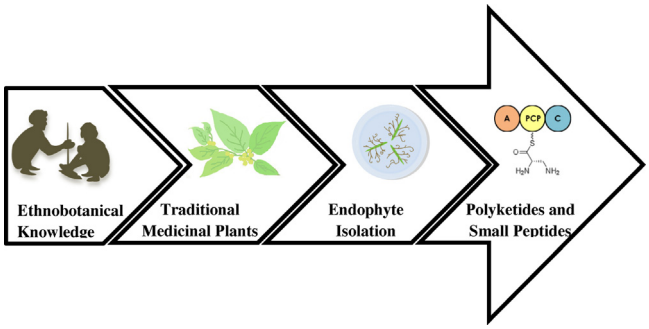

Fig. 1. Graphical representation of natural product drug discovery approach discussed in this review.

constitute almost 50% of the new drugs introduced to the market from 1981 to 2010, and approximately 75% of anti-infective agents are natural products or natural-product derivatives (Newman and Cragg, 2010). Most bioactive natural products have the ability to target specific proteins coded by essential genes (Kingston, 2011). While it is understood that this property cannot be fully utilised for human genetically linked diseases due to the more complex human protein-protein interactions (Dančík et al., 2010), this attribute has been widely explored for the treatment of infectious diseases, as these compounds are able to specifically target the infective agents (Kingston, 2011). For example, beta-lactam antibiotics, such as the penicillins and the cephalosporins, are largely used for their broad antibacterial spectrum and outstanding safety profile for human use (Danziger and Neuhauser, 2011).

Of all possible sources of natural products, plants have been viewed as one of the most promising. The plant kingdom provides a plethora of biologically active compounds, and it is estimated that only 10–15% of existing species of higher plants have been investigated (Bisht et al., 2006). Of this, only approximately 6% have been screened for biological activity (Verpoorte, 2000). Medicinal plant use can be traced to ancient agricultural societies, where indigenous populations have utilised them as therapies for many diseases (Davis, 1995). Even in the modern era, approximately 80% of the world's population, particularly those in the developing countries, still rely on herbal medicines for their primary healthcare (Gurib-Fakim, 2006). Historically, plants with healing properties have been discovered and utilised even before the cause of the disease has been fully identified. Not surprisingly, the trial and error approach has been utilised for generations in these cultures to discover plants of medicinal value.

Unfortunately, while most traditional cultures have utilised plants for medicinal purposes, this precious knowledge has generally been kept secret by traditional healers or the information is kept within their own community. The information transfer between these traditional healers and modern society is largely the result of the work by ethnobotanists, who study plant-human interrelationships in natural and social contexts (Alcorn, 1995). Since its inception, the field of ethnobotany has evolved from merely a collection of information regarding plants utilised by a particular community into a more complex, interdisciplinary research area of understanding the biological and socio-economic impacts of using the plants to the development of a particular culture.

Ethnobotanical knowledge has provided sufficient basis for further investigation of traditional plants for their medicinal properties. Modern scientists have revisited these traditional uses of the plants and carried out bioprospecting, which involves screening for natural products with biological activity (Strobel and Daisy, 2003; Ashforth et al., 2010), in order to isolate and identify the chemical entities responsible for treating diseases. Since the discovery of penicillin in 1928 (Fleming, 1929) and its mass production during World War II, modern medicine has utilised natural products as single, pharmaceutical entities and concerted efforts have been made to isolate and identify these individual bioactive compounds.

In the recent past, isolating biologically active natural products was not a preferred pathway of drug discovery as it was time consuming and resource inefficient. Nonetheless, the rate of bioassay-guided fractionation has recently been significantly improved with advances in instrumentation, such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), higher magnetic field-strength nuclear magnetic resonance (NMR) instruments, and robotic technology (Salim and Kinghorn, 2008). Compounds of limited availability in their organisms of origin are now detectable with the introduction of capillary NMR spectroscopy (Martin, 2005), while the development of automated high-throughput screening techniques have replaced bioassays as a rate-limiting step of drug discovery (Walters and Namchuk, 2003). These advances have made the list of natural products with therapeutic value ever increasing and an abundance of new compounds are continually being isolated.

Ethnobotanical knowledge has led to the isolation of novel bioactive compounds. However, plant availability is viewed to be the limiting factor in the commercial success of some natural products. At times, a large quantity of plant is required to produce sufficient amounts of the bioactive compounds for clinical use. In other cases, compounds have been isolated from endangered or highly endemic plants. This raises major concerns regarding biodiversity conservation. Plant tissue culture offers a solution (McAlpine et al., 1999), although the cost of such production methods is high. One of the advances in addressing these issues is the discovery that microorganisms residing inside the plant tissues may produce similar, if not the same, bioactive compounds as their plant hosts. From a commercial point of view, it is relatively easier to scale up the fermentation process of microbes, enabling large-scale production of biologically active compounds to meet industrial demands. These microorganisms present the opportunity to discover a plethora of compounds and offer a renewable source of natural products.

3. Endophytes as sources of natural products

Endophytes refer to the microorganisms (mostly fungi and bacteria) colonising the intercellular and intracellular regions of healthy plant tissues at a particular time, whose presence is unobtrusive and asymptomatic (Schulz and Boyle, 2006; Stone et al., 2000; Strobel, 2003). Most plant species that have been previously studied host at least one endophytic microbe (Ryan et al., 2008), with plants growing in unique environmental settings generally hosting novel endophytic microorganisms (Strobel, 2003).

Endophytes form a symbiotic relationship with their plant host. It is believed that in many cases the microbes function as the biological defence for the plant against foreign phytopathogens. The protection mechanism of the endophytes are exerted directly, by releasing metabolites to attack any antagonists or lyse affected cells, and indirectly, by either inducing host defence mechanisms or promoting growth.

Antibiotics or hydrolytic enzymes can be released by endophytes to prevent colonisation of microbial plant pathogens (Strobel, 2003; Berg and Hallmann, 2006), or prevent insects (Azevedo et al., 2000) and nematodes (Hallmann et al., 1998) from infecting plants. In other cases endophytes release metabolites which activate host defence mechanism against other pathogenic organisms, in a process known as induced systemic resistance (Kloepper and Ryu, 2006). Similarly, endophytes can also promote plant growth in an attempt to outcompete cell apoptosis induced by infecting pathogens (Berg and Hallmann, 2006). Plant growth

promotion by endophytes may be exerted by several mechanisms, such as production of phytohormones (Tudzynski, 1997), synthesis of siderophores (O'Sullivan and O'Gara, 1992), nitrogen fixation, solubilisation of minerals such as phosphorus (Richardson et al., 2009), or *via* enzymatic activities, such as ethylene suppression by 1-aminocyclopropane-1-carboxylate deaminase (Glick et al., 1998). The plant host also benefits from the endophytes by their natural resistance to soil contaminants (Siciliano et al., 2001), their ability to degrade xenobiotics, or their action as vectors to introduce degradative traits to plants, which substantially assist phytoremediation (Ryan et al., 2008).

Endophytes can produce the same or similar secondary metabolites as their host. Bioactive compounds which are co-produced by the plants as well as their associated endophytes include the anticancer drug camptothecin (Puri et al., 2005), the anticancer drug lead compound podophyllotoxin (Puri et al., 2006), and the natural insecticide azadirachtin (Kusari et al., 2012). There are several mechanisms proposed for the simultaneous production of these biological compounds. In some cases, such as that of gibberellin, the biosynthetic mechanism of the same compound evolves independently in plants and their microbial counterparts (Bömke and Tudzynski, 2009). On the other hand, horizontal gene transfer between the plant host and its endophytes have long been hypothesised, although so far this process has only been shown to occur between microbial endophytes (Taghavi et al., 2005). It has been strongly suggested, however, that interactions between endophytes and their respective plant host contributes to the co-production of these bioactive molecules (Heinig et al., 2013).

Endophytes have recently generated significant interest in the microbial chemistry community due to their immense potential to contribute to the discovery of new bioactive compounds. It has been suggested that the close biological association between endophytes and their plant host results in the production of a greater number and diversity of biological molecules compared to epiphytes or soil-related microbes (Strobel, 2003). Moreover, the symbiotic nature of this relationship indicates that endophytic bioactive compounds are likely to possess reduced cell toxicity, as these chemicals do not kill the eukaryotic host system. This is of significance to the medical community as potential drugs may not adversely affect human cells.

One of the most successful stories of natural products from endophytes is the multibillion-dollar anticancer drug Taxol (paclitaxel). The compound was initially isolated from the Pacific yew tree, *Taxus brevifolia* (Wani et al., 1971), a traditional medicinal plant used by Native Americans (Gunther, 1945). Since then, several other plants from the genus *Taxus* have been reported to produce Taxol. Nonetheless, these plants are slow-growing with generally isolated geographical distribution. Investigations of endophytes from this plant revealed that some fungi, such as *Taxomyces andreanae*, also produced the exact same compound (Stierle et al., 1995). The biological production of this compound in *Taxus* plants have been characterised (Fig. 2). While horizontal gene transfer has long been proposed for the biosynthesis of Taxol in endophytes, it has been recently showed that the endophyte genomes did not contain any sequences with significant homology to the Taxol biosynthetic genes from *Taxus* spp. (Heinig et al., 2013), indicating Taxol biosynthesis in endophytes might have developed independently from its plant host. Nevertheless, this example supports the rationale that traditional medicinal plants can be used as the starting point to investigate endophytes for their production of biologically active compounds.

As mentioned earlier, approximately three quarters of anti-infectives are natural products or natural-product derived structures. However, rather than using combinatorial chemistry to synthesise these derivatives, the biosynthesis of these natural products has been elucidated at the genetic level. As the synthesis of most of these natural products is regulated by single gene clusters, numerous research groups have attempted to isolate these clusters and utilise genetic engineering to biologically synthesise the native compounds as well as their derivatives. Two of the most studied and largest classes of secondary metabolites are the polyketides and non-ribosomal peptides (Hoffmeister and Keller, 2007).

4. Biosynthesis of natural product secondary metabolites

Peptide antibiotics constitute some of the most important anti-infective drugs on the market, most notably the β-lactams such as the penicillins and the cephalosporins (Paradkar et al., 1997). These oligopeptides are synthesised by large, multimodular enzyme complexes called non-ribosomal peptide synthetases (NRPSs), which use proteinogenic and non-proteinogenic amino acids as their building blocks. NRPSs consist of a series of modules, each consisting of catalytic units essential for amino acid recognition (adenylation domain), activation (peptidyl carrier protein), and bond formation of the growing peptide chain (condensation domain) (Fischbach and Walsh, 2006).

Variable arrangements of modules and the possible inclusion of numerous tailoring reactions have resulted in a vast array of non-ribosomal peptide scaffolds in nature. High versatility of the modules and domains in terms of both catalytic potential and interaction within the multifunctional protein templates has led to the classification of NRPS systems: linear (type A), iterative (type B), and nonlinear (type C) (Mootz et al., 2002). In linear (type A) NRPSs, the multiple modules are arranged in a sequential fashion, where each module incorporates one monomer in to the growing chain during each production cycle. In contrast, in iterative (type B) NPRS systems, the modules or domains are used multiple times in the assembly of a single product, thus creating a multimeric peptide consisting of repeated smaller sequences. The third type, non-linear (type C) NRPSs are the most sophisticated system, consisting of domains and modules organised in a non-conventional manner. The deviation from the traditional C-A-PCP arrangement is often followed by unusual internal cyclisation or branch-point syntheses, resulting in non-linear peptide products.

An example of a type A NRPS product is daptomycin, a cyclic lipopeptide which represented the first new class of antibiotics introduced in 30 years when it was approved by the Food and Drug Administration (FDA) in 2003 (Raja et al., 2003). Naturally produced by the actinomycete *Streptomyces roseosporus* NRRL11379, daptomycin consists of a cyclic core of 13 amino-acids, six of which are non-proteinogenic, and an N-terminal decanoyl lipid (Fig. 3A) (Miao et al., 2005). Valinomycin, a potent antibiotic against severe acute respiratory syndrome coronavirus, provides a good model of the type B (iterative) NRPS system. Produced by several *Streptomyces* isolates, the biosynthetic gene cluster has been isolated from *Streptomyces tsusimaensis* ATCC15141 (Fig. 3B) (Cheng, 2006). The third type, non-linear (type C) NRPSs, is responsible for biosynthesis of the potent anti-tuberculosis compound capreomycin. Isolated from *Saccharothrix mutabilis* subsp. *capreolus*, analysis of the capreomycin biosynthetic gene cluster revealed that the compound was not assembled by a typical linear or iterative NRPS mechanisms (Fig. 3C) (Felnagle et al., 2007).

Similar to the small peptides, polyketides also constitute a large proportion of industrial antibiotics. Among the most prominent examples are the polyene macrolide antibiotics, such as amphotericin B and nystatin (Gil and Martín, 1997), as well as the tetracyclines (Paradkar et al., 1997). Polyketides are natural products synthesised by polyketide synthases (PKS) which are also large multimodular enzyme complexes that function similarly to a fatty acid synthase (FAS) (Fischbach and Walsh, 2006). Resembling the NRPS system, there are three core domains in a typical PKS

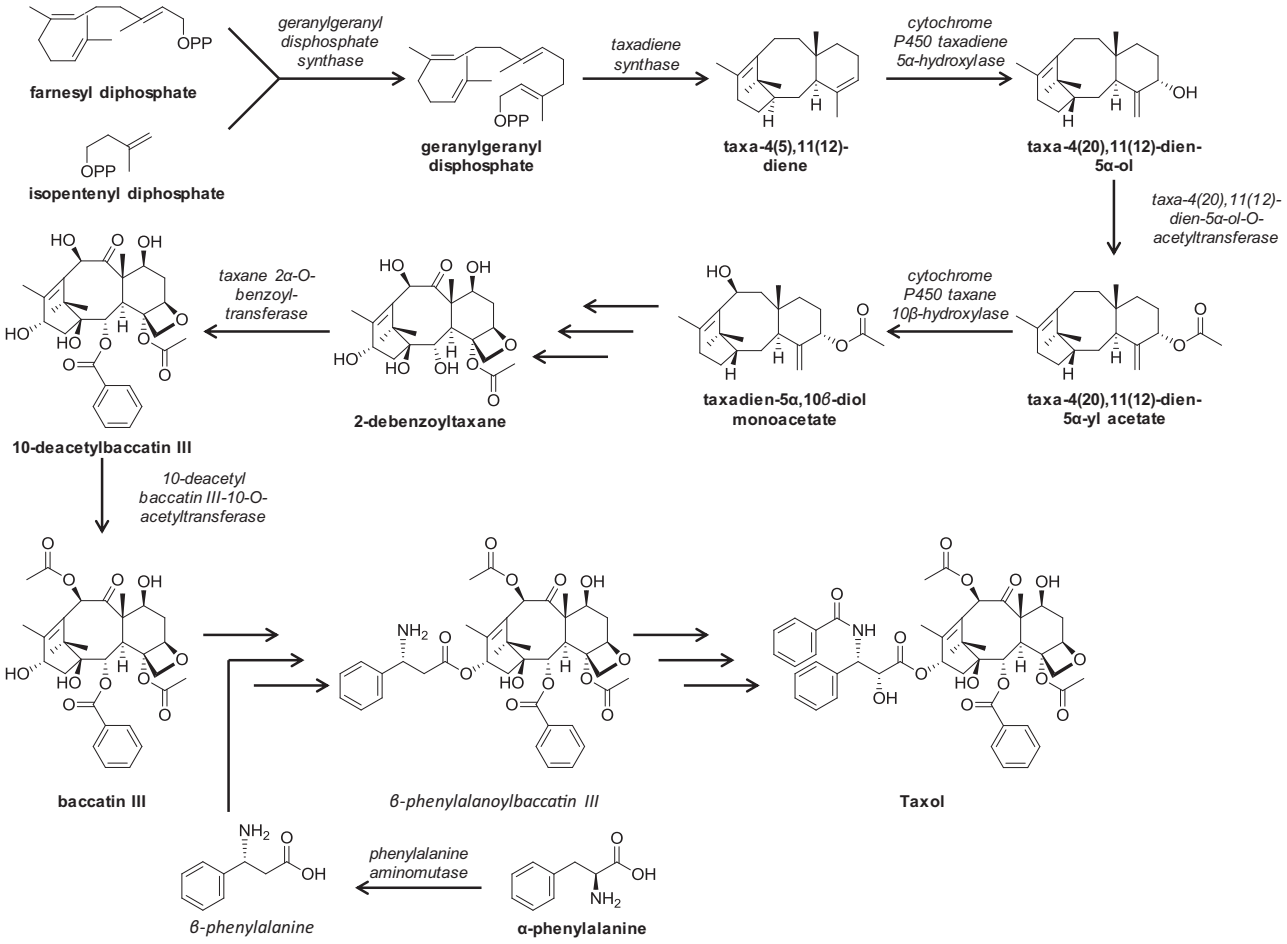

Fig. 2. Graphical representation of taxol biosynthesis in *Taxus* spp. (adapted from Walker and Croteau (2001)). Multiple arrows indicate several as yet undefined steps.

system: acyltransferase (AT), which acts as the gatekeeper for substrate specificity, selecting and activating the monomers and the intermediate acyl chain; acyl carrier proteins (ACPs), whose phosphopantetheine arm covalently attaches the growing intermediate acyl chain; and ketosynthase (KS) which catalyses C—C bond formation *via* Claisen condensation in the elongation of the polyketide chain (Fischbach and Walsh, 2006). Termination is achieved by the action of the thioesterase (TE) domain.

There are several types of PKS systems. Type I PKSs are multifunctional enzymes linearly arranged into modules, each of which consists of a set of non-iteratively acting domains responsible for the catalysis of one cycle of chain elongation (Bisang et al., 1999). Erythromycin, a broad spectrum macrolide antibiotic, is one of the most well-studied compounds of this type (Rawlings, 2001). First discovered from *Saccharopolyspora erythraea*, the compound consists of a 14-membered macrolactone ring and two glucose derived deoxysugar moieties desosamine and cladinose (3-O-methylmycarose). The construction of its precursor, 6-deoxyerythronolide B (6-deB) is controlled by a large modular protein known as 6-deB synthase (DEBS) (Fig. 4A). Type II PKSs consist of several monofunctional enzymes acting iteratively, resulting in the production of polyphenols or other aromatic polyketides (Hertweck et al., 2007). An example of this type is the anti-tumour antibiotic doxorubicin, which is produced by the actinomycete *Streptomyces peucetius* ATCC29050 (Fig. 4B) (Grimm et al., 1994). Type III PKSs, also known as chalcone synthase-like PKSs, are homodimeric enzymes consisting of multiple ACP-independent modules which essentially are iterative condensing enzymes. Biosynthesis of 2,4-diacetylphloroglucinol, an antibiotic against plant pathogens, from endophytic *Pseudomonas fluorescens* Q2-87 is known to involve a type III polyketide synthase (Fig. 3C) (Gita Bangera and Thomashow, 1999).

Plant-associated microorganisms have been found to produce novel bioactive metabolites with wide-ranging medicinal applications such as antibiotics, immunosuppressants, antiparasitics, and anticancer agents (Stierle et al., 1995). Therefore, it is hypothesised that endophytes could be useful sources of lead compounds in drug discovery. As highlighted earlier, natural products have the ability to target microbial pathogens and this is of interest to the scientific and medical communities since infectious diseases are the leading cause of human mortalities globally. One such disease which is increasingly affecting large human populations is tuberculosis. A number of natural antimycobacterials, discussed later in this review, have also been identified as PKS and NRPS products, especially those produced by bacteria or fungi.

5. Tuberculosis

Tuberculosis (TB) is a potentially deadly infectious disease caused by *Mycobacterium* sp., mainly *Mycobacterium tuberculosis*. Often infecting the lungs, it can also attack the central nervous system, the lymphatic system, as well as skeletal tissue. Common symptoms of TB include chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. TB is transmitted through the air when infected individuals cough, sneeze, or spit, spreading the bacteria from their throat or lungs.

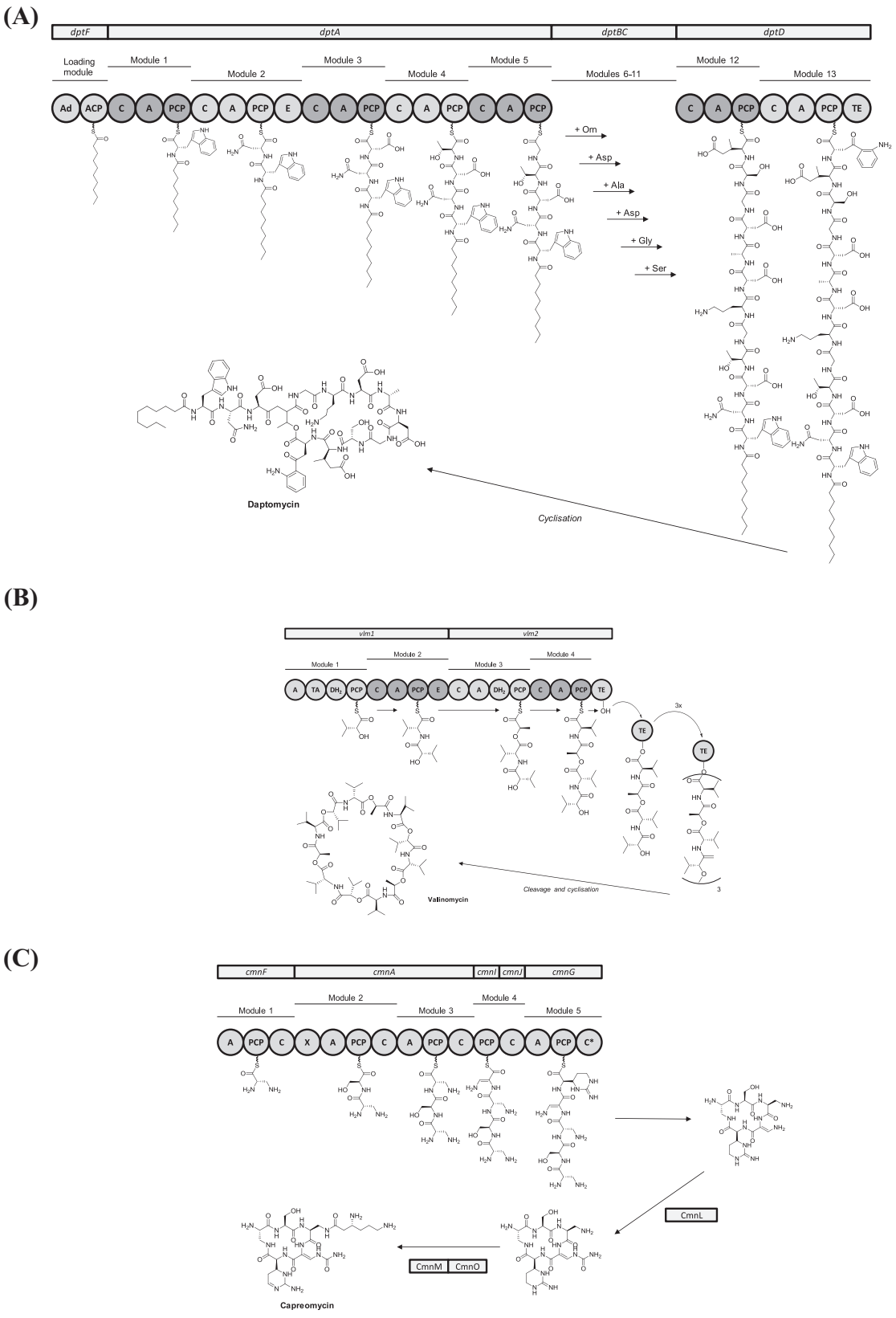

Fig. 3. Graphical representation of biosynthesis of natural bioactive compounds showing non-ribosomal peptide synthetase (NRPS). (A) Biological production of daptomycin using type A NRPS (adapted from Miao et al. (2005)). (B) Biological production of valinomycin using type B NRPS (adapted from Cheng (2006)). (C) Biological production of capreomycin using type C NRPS (adapted from Felnagle et al. (2007)). Individual NRPS domains are noted as circles with the appropriate abbreviation to indicate their function: Ad = adenylating enzyme, PCP = peptidyl carrier protein, C = condensation domain, A = adenylation domain, E = epimerisation domain, TE = thioesterase domain, TA = transaminase domain, DH_2 = dehydrogenation domain, X = domain with no known function, C* = modified condensation domain. The genes or protein responsible for a particular process are noted as boxes.

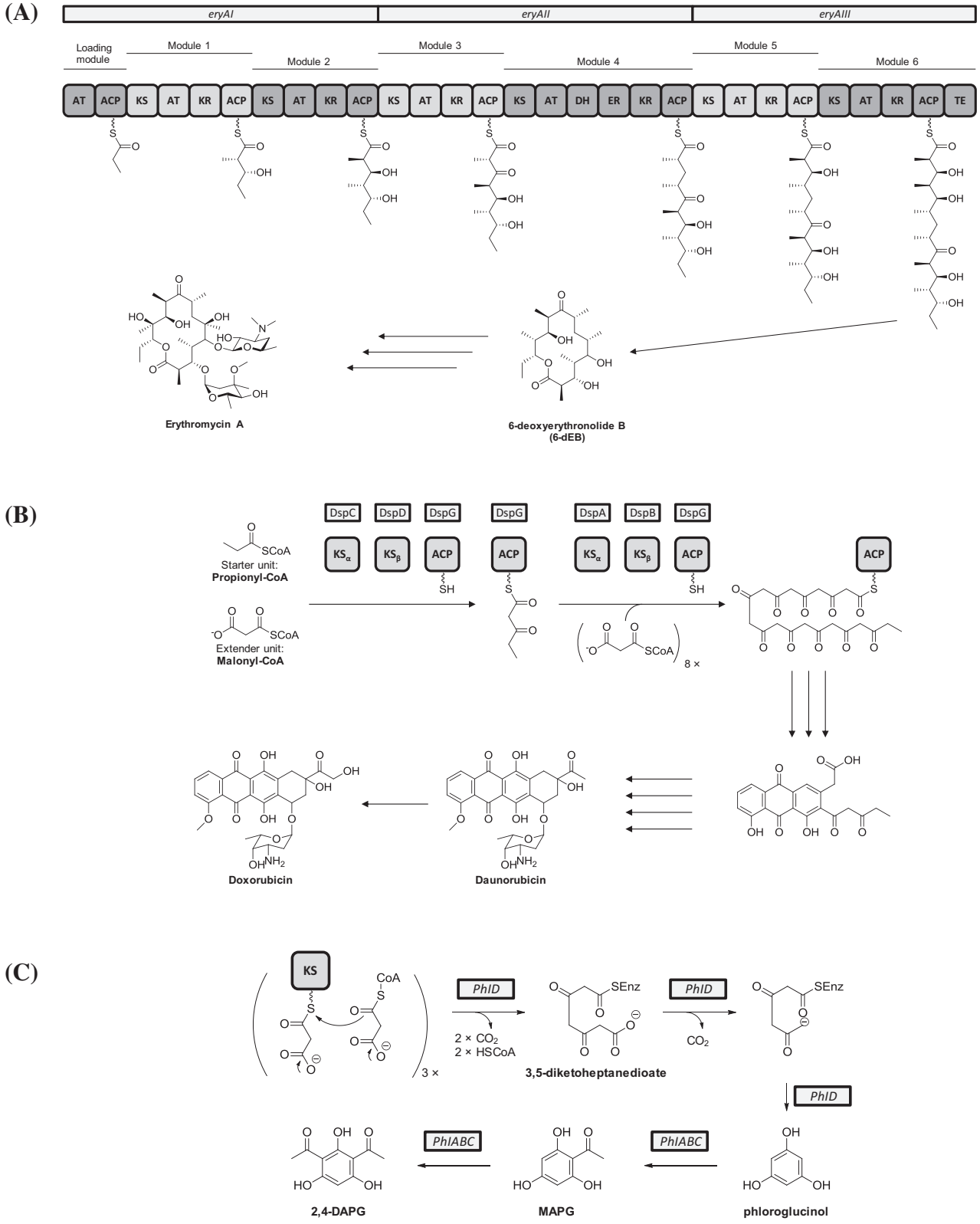

Fig. 4. Graphical representation of biosynthesis of natural bioactive compounds showing polyketide synthase (PKS). (A) Biological production of erythromycin, highlighting Type I PKS in the formation of 6-deoxyeryhtronolide B, its precursor (adapted from Cane (2010)). (B) Biological production of doxorubicin using Type II PKS (adapted from Chan et al. (2009)). (C) Biological production of 2,4-diacetylphloroglucinol using Type III PKS (adapted from Gross and Loper (2009)). The individual PKS domains are noted as curved rectangle with the appropriate abbreviation to indicate their function: AT = acyltransferase domain, ACP = acyl carrier protein, KS = ketosynthase domain, KR = ketoreductase domain, DH = dehydratase domain, ER = enoylreductase domain, KS_α = ketosynthase domain which catalyses decarboxylative Claisen condensation of the precursors, KS_β = ketosynthase domain which controls the polyketide length. The genes or protein responsible for a particular process are noted as boxes.

Table 1
Mechanism of action and causes of resistance development of various anti-tuberculosis chemotherapeutic agent.

Chemotherapeutic agent	Mechanism of action	Resistance development
Aminoglycosides: amikacin, kanamycin, streptomycin	Inhibition of protein synthesis, particularly in translational initiation (Pestka, 1977)	Acquisition of aminoglycoside-inactivating enzymes (Shaw et al., 1993), mutational alteration of target structural gene *rrs* (Alangaden et al., 1998) or ribosomal protein (Finken et al., 1993)
D-cycloserine (cyclic analogue of D-alanine)	Inhibition of cell wall biosynthesis (Halouska et al., 2007)	Overexpression of target gene *alrA* (Cáceres et al., 1997)
Ethambutol	Inhibition of cell wall biosynthesis (Wolucka et al., 1994; Lee et al., 1995)	Mutation in the target operon *embCAB*, particularly the gene *embB* (Ramaswamy et al., 2000)
Ethionamide and prothionamide (structural analogue of isoniazid)	Inhibition of cell wall, particularly mycolic acid, biosynthesis (Banerjee et al., 1994; Baulard et al., 2000)	Mutation in the target gene *inhA* (Banerjee et al., 1994); overexpression of EthR, a repressor of ethionamide activator (Engohang-Ndong et al., 2004)
Fluoroquinolones: ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin	Inhibition of DNA replication (Drlica and Zhao, 1997)	Mutation in target genes *gyrA* (Drlica and Zhao, 1997; Alangaden et al., 1995) and *gryB* (Aubry et al., 2006)
Isoniazid	Inhibition of fatty acid biosynthesis (Banerjee et al., 1994; Takayama et al., 1975; Rozwarski et al., 1998)	Mutation in *katG* gene to prevent drug activation (Zhang et al., 1992) and mutation in the target structural gene *inhA* (Rouse et al., 1995; Bergval et al., 2009)
Isoxyl	Inhibition of mycolic acids, oleic acid, tuberculostrearic acid, and other short-chain fatty acids biosynthesis (Phetsuksiri et al., 2003)	Mutation in the target gene *etaA*, and possible cross-resistance between thiocarbonyl-containing antibiotics (DeBarber et al., 2000)
Macrolides: erythromycin, clarithromycin, roxithromycin	Inhibition of protein synthesis, particularly in translational initiation (Taubman et al., 1966)	Point mutations in the target 23S rRNA gene (Meier et al., 1994; Nakajima, 1999); increased expression of *ermMT* gene resulting in substantial loss of drug binding (Andini and Nash, 2006)
Oxazolidinones: linezolid, eperezolid, DA-7157, DA-7218, DA-7867	Inhibition of protein synthesis, particularly in translational initiation (Shinabarger et al., 1997)	Alteration in the efflux pump or drug transport mechanism (Richter et al., 2007)
p-Aminosalicylic acid	Inhibition of folate (Rengarajan et al., 2004) and thymine nucleotides (Mathys et al., 2009) biosynthetic pathways	Mutations in the target gene *thyA*, though the major cause is yet to be identified (Mathys et al., 2009)
Phenothiazines: thioridazine, chlorpromazine, trifluoperazine	Inhibition of cell wall biosynthesis, lipid metabolism (Reddy et al., 1996), and oxidative phosphorylation (Yano et al., 2006)	Yet to be identified (Amaral, 2012)
Pyrazinamide (synthetic analogue of nicotinamide)	Mechanism not fully understood, though it is thought to be inhibiting vital enzyme activities and disrupting membrane transport (Heifets and Lindholm-Levy, 1992; Zhang et al., 1999; Zhang and Mitchison, 2003)	Mutation in the gene *pncA*, preventing drug activation (Scorpio et al., 1997)
Rifamycins: rifampin, rifabutin, rifalazil, rifapentine	Inhibition of protein synthesis, particularly in transcriptional initiation (Kunin, 1996) and induction of programmed cell death (Engelberg-Kulka et al., 2004)	Mutation in the target structural gene *rpoB* (Telenti et al., 1993)
Riminophenazines: clofazimine, B746, B4157	Disruption to potassium transport (Cholo et al., 2006) and electron transport involved in cellular respiration (Boshoff et al., 2004)	Yet to be identified (Xu et al., 2011)
Thiacetazone	Disruption of cell envelope permeability and host immunomodulation (Alahari et al., 2009)	Mutation in the gene *ethA* (DeBarber et al., 2000); possible cross-resistance between thiocarbonyl-containing antibiotics (DeBarber et al., 2000)
Tuberactinomycin: enviomycin/tuberactinomycin N, viomycin, capreomycin	Inhibition of protein synthesis, particularly in post-transcriptional modification and translational initiation (Thomas et al., 2003; Liou and Tanaka, 1976; Wank et al., 1994)	Single and double mutations in target ribosomal subunit genes (Felnagle et al., 2007; Yamada et al., 1978; Taniguchi et al., 1997)

One–third of the world's current population have been infected with *M. tuberculosis* (Koul et al., 2011). There were approximately 8.8 million reported cases of active TB in 2010, 5.7 million of which are new or relapsed cases. The disease caused approximately 1.5 million deaths (World Health Organization, 2011). Though TB incidence is more common in developing and under-developed countries (World Health Organization, 2011), the rising frequency of population migration has resulted in increased occurrences in developed countries.

6. Current anti-tuberculosis therapies

In most cases, TB is curable, provided that the drug regime is followed diligently (Frieden et al., 2003). An anti-TB drug regime is considered successful if all mycobacteria are killed, preventing patient relapse after cessation of treatment, and avoiding the development of drug resistant mycobacteria. As there are naturally occurring drug-resistant mycobacteria at any stage of the infection, it is currently impossible to treat the disease with a single drug (Grosset, 1996).

Drugs that are commonly used to treat TB are listed in Table 1. A typical drug regime comprises a combination of bactericidal and bacteriostatic drugs. Since the 1950s, the standard first-line therapy for tuberculosis involves a two month treatment with a combination of rifampicin, isoniazid, ethambutol, and pyrazinamide, followed by treatment with a combination of rifampicin and isoniazid for an additional four months (Grosset, 1996). Unfortunately, stringent drug therapy is not accessible to most sufferers, particularly those in high burden countries in Asia and Africa. Incomplete treatment of the disease causes the development of drug-resistant TB.

M. tuberculosis has intrinsic drug resistance mechanisms that render most antimicrobials ineffective. Its unique lipid-rich cell envelope structure has low permeability to most clinical antibiotics (Jarlier and Nikaido, 1994), and it is equipped with drug efflux pumps (Louw et al., 2009). Provided that the drug is able to penetrate the cell wall, mycobacteria have another complementary system that coordinates resistance to antibiotics inhibiting cytoplasmic targets. On the other hand, *M. tuberculosis* is known to possess genomic plasticity (Domenech et al., 2001). Most cases of drug resistance in *M. tuberculosis* develop *via* mutations of the

Table 2
Anti-tuberculosis drug candidates in clinical trials.

Drug	Sponsor	Class	*In vitro* potency	Mode of action	Clinical trial status
TMC 207 (Bedaquiline)	Janssen	Diarylquinoline	30–120 ng/ml (Andries et al., 2005; Koul et al., 2008)	Targeting ATP synthase, inhibition of proton pumping activity (Huitric et al., 2010)	III, FDA-approved (accelerated programme) (Cohen, 2013)
PA-824	TB Alliance	Nitroimidazole	150–300 ng/ml (Stover et al., 2000)	Prevention of cell wall mycolic acid biosynthesis (Singh et al., 2008; Maroz et al., 2010; Manjunatha et al., 2006, 2009)	II (Jones, 2013)
OPC 87863 (Delamanid)	Otsuka	Nitroimidazole	6–24 ng/ml (Matsumoto et al., 2006)	Prevention of cell wall mycolic acid biosynthesis (Gler et al., 2012)	III (Jones, 2013)
SQ109	Sequella	Ethylenediamine	200–780 ng/ml (Sacksteder et al., 2012)	Inhibition of mycolic acid transport to the cell wall (Boshoff et al., 2004; Tahlan et al., 2012)	II (Sacksteder et al., 2012)
PNU-100480 (Sutezolid)	Pfizer	Oxazolidinone	120 ng/ml (Barbachyn et al., 1996)	Targeting 23S rRNA, inhibition of bacterial protein synthesis (Patel et al., 2001)	II (Jones, 2013)
AZD5847	AstraZeneca	Oxazolidinone	-Undisclosed data-	-Undisclosed data-	II (Jones, 2013)

target genes, such as *rpoB* against rifampicin, *rrs* against kanamycin, and *gyrA* against the fluoroquinones. Multidrug resistance occurs *via* the accumulation of independent mutations in more than one of these genes (Rattan et al., 1998).

One of the major issues in antimycobacterial research is the absence of new drugs with novel mechanisms of action, while resistance has been observed with all current therapeutics. Cutting-edge technologies and more advanced screening processes have resulted in several drug candidates with novel activities currently being tested in later stage clinical trials (Table 2). From these new drug candidates, the semi-synthetic TMC207 has received FDA approval, specifically for patients with MDR-TB, through its accelerated approval programme which based its decision on Phase II trials (Cohen, 2013; Diacon et al., 2009, 2012). Commercialised under the name bedaquiline, it is the first anti-TB therapy with a novel mechanism of action in more than 40 years (Osborne, 2013).

7. The search for new anti-tuberculosis natural products

Natural products have played crucial roles in the treatment of TB. The global effort to decrease the incidence of TB, combined with the rapid development of resistant strains, has increased interest in natural products as sources of novel anti-tubercular compounds. Development of *in vitro* whole organism reporter bioassays (Changsen et al., 2003), purified target (biochemical) bioassays (Schaeffer et al., 2004; Scherman et al., 2003), and *in vivo* bioassays (Lenaerts et al., 2003) have accelerated the assessment process for drug candidates, and thus considerably increased the discovery rate of new compounds.

More than 300 novel anti-tubercular agents were identified and characterised from biological sources between 2003 and 2005 (Copp and Pearce, 2007), while there were a further 450 novel entities identified from 2006 to 2009 (Salomon and Schmidt, 2012). Furthermore, there have been 28 novel compounds isolated from microbial sources between 2008 and 2012, as listed in Table 3. Of these, 11 were polyketides or polyketide-derived, and 10 were small peptides, further highlighting the significance of these classes of natural products.

Natural product drug discovery works on the basis that biological diversity is the key to chemical diversity (Singh and Pelaez, 2008). One prerequisite for the discovery of novel bioactive compounds is choosing suitable source material which significantly increases the chance of "hitting a target". Plants have long been viewed as a common source of remedies, either in the form of traditional preparations or as pure active principles. This forms a strong basis to utilise local plants that have been traditionally used as medicine and investigate them for their active chemical constituents. In fact, Norman R. Farnsworth, one of the pioneers in the field of pharmacognosy (study of traditional medicines), highlighted that in 1985, there were 119 compounds isolated from 90 plants which were utilised as single entity medicinal agents (Farnsworth et al., 1985). Most importantly, 77% of these compounds were obtained as a result of examining the plant based on an ethnomedical use, and were utilised in a manner similar to their traditional use. This emphasises the rationale of investigating traditional medicinal plants for chemical discovery.

Additionally, to further increase chemical diversity, and based on the premise that each plant hosts a number of endophytic microorganisms, it has been beneficial exploring these microbes to discover novel compounds. An example is provided by a group of microbiologists in Thailand, who investigated fungal endophytes from their local medicinal plants for bioactivity (Wiyakrutta et al., 2004). It was shown that from 360 morphologically distinct endophytic fungi, extracts from 92 isolates were found to inhibit the growth of *M. tuberculosis* $H_{37}Ra$ (MIC of 0.0625–200 μg/ml), 6 inhibited *Plasmodium falciparum* (IC_{50} of 1.2–9.1 μg/ml), 40 showed antiviral activity against Herpes simplex virus type I (IC_{50} of 0.28–50 μg/ml), 60 exhibited anti-proliferative activity against a human oral epidermoid carcinoma cell line (EC_{50} of 0.42–20 μg/ml), and 48 extracts had anti-cancer activity against breast cancer cells (EC_{50} of 0.18–20 μg/ml). These examples highlight the mutual relationship between biological diversity and drug discovery.

Endophytes are a potential source of novel bioactive compounds. Nonetheless, fine screening, purification, and identification methods are required to target active compounds since each microorganism may contain a large pool of compounds with only few being bioactive. An example is the culturable endophytes from traditional Chinese medicinal plants (Miller et al., 2012). Bacterial and fungal endophytes from eight plants, traditionally used for anticancer therapy, were screened genetically for the presence of PKS and NRPS systems. Assays investigating antibacterial, antifungal, and cytotoxicity traits were also performed using crude extracts from these endophytes. The eight plants hosted 74 bacterial endophytes belonging to 14 genera, as well as 36 fungal endophytes from 10 genera. Moreover, 12% of bacterial endophytes and 58% of fungal endophytes possessed PKS machinery, while 13% of bacterial endophytes and 17% of fungal endophtyes had at least NRPS gene cluster. All of the endophytes equipped with either PKS and/or NRPS system exhibited anti-proliferative effects in at least one bioassay. From this example, it was shown that traditional medicinal plants harbour endophytes producing bioactive natural products. There was

Table 3
Novel microbial antitubercular compounds from 2008–2012.

Compound	Class	Microbial producer	Active against	MIC	Refs.
Phomoenamide	Amide	*Phomopsis* sp. PSU-D15	*M. tuberculosis* H37Ra	6.25 μg/ml	(Rukachaisirikul et al., 2008)
Bisdethiobis(methylsulfanyl) apoaranotin	Peptide	*Aspergillus terreus* BCC 4651	*M. tuberculosis* H37Ra	25 μg/ml	(Haritakun et al., 2012)
Calpinactam	Peptide	*Mortierella alpine* FKI-4905	*M. tuberculosis* H37Rv	12.5 μg/ml	(Koyama et al., 2010)
Cordycommunin	Peptide	*Ophiocordyceps communis* BCC 16475	*M. tuberculosis* H37Ra	15 μM	(Haritakun et al., 2010)
Nocardithiocin	Peptide	*Nocardia pseudobrasiliensis* IFM 0757	*M. tuberculosis* H37Rv	0.025 μg/ml	(Mukai et al., 2009)
Sansanmycin A	Peptide	*Streptomyces* sp. SS	*M. tuberculosis* H37Rv	16 μg/ml	(Xie et al., 2010)
Sansanmycin F	Peptide	*Streptomyces* sp. SS	*M. tuberculosis* H37Rv	16 μg/ml	(Xie et al., 2010)
Sansanmycin G	Peptide	*Streptomyces* sp. SS	*M. tuberculosis* H37Rv	16 μg/ml	(Xie et al., 2010)
Trichoderin A	Peptide	*Trichoderma* sp. 05F148	*M. tuberculosis* H37Rv	0.12 μg/ml	(Pruksakorn et al., 2010)
Trichoderin A1	Peptide	*Trichoderma* sp. 05F148	*M. tuberculosis* H37Rv	2.0 μg/ml	(Pruksakorn et al., 2010)
Trichoderin B	Peptide	*Trichoderma* sp. 05F148	*M. tuberculosis* H37Rv	0.13 μg/ml	(Pruksakorn et al., 2010)
(3S,4R)-4,8-Dihydroxy-3-methoxy-3,4-dihydronaphthalen-1(2H)-one	Polyketide	*Phaeosphaeria* sp. BCC 8292	*M. tuberculosis* H37Ra	12.5 μg/ml	(Pittayakhajonwut et al., 2008)
(4S)-3,4,8-Trihydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one	Polyketide	*Phaeosphaeria* sp. BCC 8292	*M. tuberculosis* H37Ra	25 μg/ml	(Pittayakhajonwut et al., 2008)
(S)-4,6,8-Trihydroxy-3,4-dihydronaphthalen-1(2H)-one	Polyketide	*Phaeosphaeria* sp. BCC 8292	*M. tuberculosis* H37Ra	12.5 μg/ml	(Pittayakhajonwut et al., 2008)
1-(1-Hydroxy-3,6-dimethoxy-5,8-dioxo-5,8-dihydronaphthalen-2-yl)ethyl acetate	Polyketide	*Phaeosphaeria* sp. BCC 8292	*M. tuberculosis* H37Ra	0.39 μg/ml	(Pittayakhajonwut et al., 2008)
2,5,7-Trihydroxy-3-(1-(1-hydroxy-3,6-dimethoxy-5,8-dioxo-5,8-dihydronaphthalen-2-yl)ethyl)naphthalene-1,4-dione	Polyketide	*Phaeosphaeria* sp. BCC 8292	*M. tuberculosis* H37Ra	6.25 μg/ml	(Pittayakhajonwut et al., 2008)
6-Ethyl-5-hydroxy-2,7-dimethoxynaphthalene-1,4-dione	Polyketide	*Phaeosphaeria* sp. BCC 8292	*M. tuberculosis* H37Ra	12.5 μg/ml	(Pittayakhajonwut et al., 2008)
Biscogniazaphilone A	Polyketide	*Biscogniauxia formosana*	*M. tuberculosis* H37Rv	5.12 μg/ml	(Cheng et al., 2012)
Biscogniazaphilone B	Polyketide	*Biscogniauxia formosana*	*M. tuberculosis* H37Rv	2.52 μg/ml	(Cheng et al., 2012)
Chaetoviridine E	Polyketide	*Chaetomium cochloides* VTh01	*M. tuberculosis* H37Ra	50 μg/ml	(Phonkerd et al., 2008)
Mollicellin K	Polyketide	*Chaetomium brasiliense*	*M. tuberculosis* H37Rv	12.5 μg/ml	(Khumkomkhet et al., 2009)
Ramariolide A	Polyketide	*Ramaria cystidiophora* W179	*M. tuberculosis* H37Rv	64 μg/ml	(Centko et al., 2012)
3-*epi*-astrahygrol	Terpene	*Astraeus pteridis*	*M. tuberculosis* H37Rv	34 μg/ml	(Stanikunaite et al., 2008)
3-*epi*-astrapteridiol	Terpene	*Astraeus pteridis*	*M. tuberculosis* H37Rv	58 μg/ml	(Stanikunaite et al., 2008)
Astraodoric acid A	Terpene	*Astraeus odoratus*	*M. tuberculosis* H37Ra	50 μg/ml	(Arpha et al., 2012)
Astraodoric acid B	Terpene	*Astraeus odoratus*	*M. tuberculosis* H37Ra	25 μg/ml	(Arpha et al., 2012)
Hopane-6b,11a,22,27-tetraol	Terpene	*Conoideocrella tenuis* BCC 18627	*M. tuberculosis* H37Ra	52 μM	(Isaka et al., 2011)
Ramiferin	Terpene	*Kionochaeta ramifera*	*M. tuberculosis* H37Ra	12.7 μM	(Bunyapaiboonsri et al., 2008)

Table 4
Indonesian plants that were traditionally used to treat symptoms of tuberculosis.

Plant	Local name	Parts used	Medicine preparation
Andrographis paniculata	Sambiloto	Leaves	Ground with mortar and pestle, served with honey (Dalimartha, 1999)
Brucea javanica	Buah Makasar	Fruit	Ground with mortar and pestle (Dalimartha, 2000)
Caesalpinia sappan	Secang	Stem	Boiled water extract of chopped pieces (Dalimartha, 2009)
Centella asiatica	Pegagan	All aerial parts	Boiled water extract of ground plant (Dalimartha, 2000)
Hibiscus tiliaceus	Waru	Leaves	Boiled water extract (Dalimartha, 2000)
Lantana camara	Tembelekan	Leaves and flowers	Boiled water extract (de Padua et al., 1999)
Morinda citrifolia	Mengkudu	All aerial parts	Boiled water extract (Dalimartha, 2006)
Nasturtium indicum	Sawi Tanah	All aerial parts	Boiled water extract (Dalimartha, 2009)
Pluchea indica	Beluntas	Leaves and roots	Boiled water extract (Dalimartha, 1999)
Rhoeo spathacea	Nanas Kerang	Leaves	Boiled water extract (Dalimartha, 2003)
Ricinus communis	Jarak	Leaves and roots	Boiled water extract (Dalimartha, 2008)
Vitex trifolia	Legundi	Leaves	Boiled water extract (Dalimartha, 2008)

also a strong correlation between PKS/NRPS genes and bioactivity. Thus, combining genetic- and bioactivity-based de-replication steps, a streamlined method for bioactive natural product discovery was developed.

8. Indonesian traditional medicine for the treatment of tuberculosis

Indonesia has one of the world's largest floral diversities. This is largely due to its complex geological history, the existence of a large number of islands with endemic species, and the tropical climate that supports the growth of a diverse range of plants. Indonesia contains two of the world's 25 biodiversity hotspots, the Sundaland and Wallacea regions, and has more than 40,000 different plant species, 16,500 of which are endemic (Myers et al., 2000). Of these plant species, approximately 10% are believed to possess some medicinal characteristics (Schumacher, 1999), many of which have not been investigated. Indonesian traditional herbal medicine, collectively referred to as *jamu*, has achieved a worldwide reputation for their use in treating various diseases. Approximately three-quarters of the country's population consume various types of *jamu* on a regular basis for healthcare (Steffan et al., 2005). As with all traditional medicines, the development of *jamu* started by random experiments to discover the beneficial properties of plants (Stevensen, 1999). The traditional healers, who possessed advanced knowledge of these plants, have occupied a privileged position in society (Schumacher, 1999). The knowledge has mainly passed verbally from generation to generation (Limyati and Juniar, 1998).

Ethnobotanical drug discovery efforts resulted the discovery of the polyphenols from two frequently used traditional Indonesian medicinal plants (Steffan et al., 2005). *Guazuma ulmifolia* Lam. (local name: daun jati belanda) was traditionally used to treat liver disease, while *Sauropus androgynus* Merr. (local name: daun katuk) reduces fever. Researchers believed that the beneficial effects of these plants were associated with the antioxidative activity of polyphenols. Subsequent phytochemical investigations isolated kaempferol from *S. androgynus* and luteolin from *G. ulmifolia*. The antioxidative properties of these compounds were confirmed by *in vitro* tests using rat hepatoma cells.

As with other cultures around the world, a number of plants have been utilised by Indonesian traditional herbalists to treat what commonly know as TB (Table 4). It is worth noting that as knowledge of the disease was limited, the plants used in traditional therapies for what we now know as TB were based on the symptoms the patients exhibited, such as coughing with blood-tinged sputum or shortness of breath. While a small proportion of Indonesian medicinal plants have been extensively studied and contain specific anti-tubercular compounds, most of these plants remain under-studied and may be host to many endophytes and their antibiotics compounds.

9. Concluding remarks

There is a persistent battle between pathogens and drugs and thus, a constant urgency to discover novel antibiotics against these microorganisms, particularly the rapidly developing drug resistant strains of *M. tuberculosis*. The critical first step in discovering novel bioactive compounds is pin-pointing the most suitable source material. According to Professor Gary Strobel, one of the pioneers of endophyte studies, there are three important criteria for bioprospecting: significant biodiversity, a history of long-term human habitation, and the presence of native healers with a knowledge of local medicinal plants (Gordon, 2007).

Home to some of the largest tropical rainforests in the world, Indonesia offers an incredible range of biodiversity, most of which has never been investigated. Biological diversity often translates into molecular diversity, increasing the possibility of isolating new chemical entities. Utilising traditional knowledge by studying plants that have been used to treat symptoms of respiratory disease may assist in narrowing down the plants as targets for investigating the production of novel antimycobacterial compounds. Furthermore, based on the premise that many plant bioactive compounds are actually produced by their microbial symbionts, exploring the endophytes from these medicinal plants will assist in isolating and producing their active components.

The ultimate aim of bioprospecting for novel compounds is to isolate compounds which are safe and efficacious for human use. Efficient screening mechanisms are crucial for targeting potential bioactive compounds. Prior knowledge of biosynthesis of polyketides and small non-ribosomal peptides greatly assists in de-replicating the plethora of compounds produced by a single microorganism. Structure elucidation of the isolated chemicals and characterisation of their biosynthetic pathways provides a basis for these novel compounds to be investigated in clinical trials and for commercial purposes. The potential of antimycobacterial drug discovery from endophytes from traditional medicinal plants is immense.

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