Endophytic bacteria as a source of novel antibiotics: An overview

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ABSTRACT

World human population is increasing with an alarming rate; and a variety of new types of health issues are popping up. For instance, increase in number of drug-resistant bacteria is a cause of concern. Research on antibiotics and other microbial natural products is pivotal in the global fight against the growing problem of antibiotic resistance. It is necessary to find new antibiotics to tackle this problem. The use of therapeutic plant species in traditional medicine is as old as mankind; and currently, it is strongly believed that all types of plant species across the plant kingdom do harbour endophytic bacteria (EB). The natural therapeutic compounds produced by EB do have several potential applications in pharmaceutical industry. The EB derived natural products such as Ecomycins, Pseudomycins, Munumbicins and Xiamycins are antibacterial, antimycotic and antiplasmodial. Some of these natural products have been reported to possess even antiviral (including Human Immunodeficiency Virus (HIV)) properties. Therefore, to deal with increasing number of drug-resistant pathogens EB could serve as a potential source of novel antibiotics.

Key words: Bioprospecting, ecomycins, human immunodeficiency virus, kakadumycins, medicinal plants, munumbicins, natural products, pseudomycins, traditional medicine, xiamycins

INTRODUCTION

Endophytes are micro-organisms (bacteria and fungi) that live inside the living plant tissues for at least part of their life without causing any apparent disease symptoms in the host.[1] Endophytes are treated as endosymbiont. To represent these types of micro-organisms, De Bary[2,3] coined the term endophyte. Endophytes have been reported in many important medicinal plants, weeds, and ornamental and fruit trees from wild and domesticated settings. Both endophytic bacteria and endophytic fungi can co-exist in a single host plant.[4] The population of endophytes is considered as a subset of the rhizospheric microbial population as reported by Germida *et al*.[5] Endophytes enter inside plants primarily through the roots and the aerial portions of plants, such as leaves, flowers, stems and cotyledons.[6] They are localized at the point of entry and can spread in the whole host plant body.[7] After entering the host, they reside within cells or the intercellular spaces or in the vascular (tissue) system.[8-10] After gaining residence in the plant tissues, the endophytes are known to produce a diverse range of natural products which could be consistent and successful source of drugs. Therefore, the natural products from endophytic microbes do have a great potential not only in pharmaceutical industry but agrochemical and biotechnology industries also.[11]

The natural products obtained from endophytic microbes are found to be antimicrobial, antiviral, anticancer, antioxidants, antidiabetic and immunosuppressant.[12-19] The fungal endophytes are known to produce these types of natural products. Nonetheless, poorly explored and underutilized EB are known to produce antibiotics in addition to other natural products. The EB appears to be a potential source of novel antibiotics. It is well known fact that until now the soil bacteria have been the source for most of the antibiotics. Now the EB seem to be a promising alternative potential source of novel antibiotics. This article aims to provide an overview in

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brief on bacterial endophytes as a potential source of novel antibiotics.

MAIN TYPES OF EB

In general, EB are divided into two main types namely, obligate and facultative.[20] Facultative endophytes are capable to survive in the soil, on the plant surface, inside the plants as well as on artificial nutrients[20] and endophytes which inhabit inside plant tissues throughout their lifespan are called as obligate endophytes.[21] Uncultivable EB are also reported from several plant species and plantlets from *in vitro* cultures. Facultative EB (cultivable) are widely distributed across the plant kingdom and can be isolated from various plant species to explore their potential for the production of commercially important natural products.

DISTRIBUTION OF EB

Several species of cultivable EB (including both gram-positive and gram-negative) have been isolated, identified and reported from a large diverse terrestrial and aquatic plants.[22-24] The EB do not get any benefit from their host plant other than residency[25] and nutrients. It is important to note that population density of EB remains very low in comparison to that of rhizospheric bacteria or plant pathogenic bacteria. A very comprehensive lists of EB isolated from a broad range of plant species are available in public domain.[7,26] In our laboratory, we have also isolated and identified more than 1280 isolates of cultivable EB from various plant species available in Malaysia (our unpublished data at http://www.ncbi.nlm.nih.gov/nuccore/?term=bhore%20sj.[27-29] The systematic primary analysis of isolates suggests that EB are widely distributed in monocotyledonous and dicotyledonous plant species.

ROLES OF EB

The endophytes are known to boost the growth and development of host plants in varied environmental and ecological conditions.[30-32] The EB are also known to increase host plants resistance to pathogens and to promote biological nitrogen fixation as stated by Bhore *et al*.[27] However, the ability of EB to produce various natural products is of prime importance in pharmaceutical industry.[33] To explore EB, a number of research teams worldwide are involved in screening of endophytes for various natural products (bioactive compounds). Several EB have been shown to produce natural products like phytohormones, low molecular weight compounds, enzymes, siderophores, and antibiotics.[24,27,34-38]

ENDOPHYTES AS A SOURCE OF ANTIBIOTICS

The human population is increasing with an alarming rate; ecosystems are deteriorating rapidly; and a variety of new types of health issues are popping up. For instance, increase in number of drug-resistant bacteria is a cause of concern. Research on antibiotics and other microbial natural products is pivotal in the global fight against the growing problem of antibiotic resistance. It is necessary to find new antibiotics to tackle this problem; and EB are one of the potential sources of novel antibiotics.

Natural products are metabolites from micro-organisms, plants and animals.[39] These natural products are important, because they have been the traditional sources of drugs. In many cases, natural products have served as sources of lead molecules, which yielded many synthetic drugs. The world's first billion-dollar anticancer-drug, paclitaxel (Taxol) is an outstanding example of a natural product from Yew tree, *Taxus wallachiana*.[40] In 1996, Strobel *et al*. reported that endophytic fungus (*Pestalotiopsis microspora*) found in Yew tree is also able to produce Taxol.[41] The classical immunosuppressive cyclosporine isolated from the endophytic fungus (*Tolypocladium inflatum*) further increased the importance and significance of endophytes.[19,42-43] Like endophytic fungi, EB also have amazing potential in producing novel natural products. In fact, researchers are working in that direction to explore EB for the novel and unique natural products of commercial importance. Many natural products produced by endophytes have proven to be antibacterial, antifungal, antidiabetic, antioxidants and immunosuppressives. Thus, endophytes are viewed as a great source of bioactive natural products. The majority of EB do produce different kinds of antibiotics; and in fact, the EB are one of the untapped potential sources of novel antibiotics. Ecomycins, Pseudomycins, Munumbicins, Kakadumycins are some examples of the novel antibiotics produced by EB.

ECOMYCINS

The Ecomycins represent a family of novel lipopeptides and are made up of some unusual amino acids including homoserine and β-hydroxy aspartic acid. The Endophytic bacterium, *Pseudomonas viridiflava* is known to produce Ecomycins.[44] This endophyte is one of the plant-associated fluorescent *Pseudomonads*; and it is known to exist in the tissues of many grass species. The identified and partially characterized three antifungal lipopeptides produced by *P. viridiflava* strain EB273 are called as Ecomycin A, B and C. Out of these three molecules, the Ecomycin A is similar to (amino acid composition) an already reported antibiotic syringotoxin.[45] Conversely, Ecomycin B and C represent a unique set of related lipopeptides in not possessing phenylalanine, lysine, arginine, ornithine or diaminobutyric acid, which are constituents of such compounds as the pseudomycins, syringomycins, syringostatins and syringotoxin.[45-48] Further, studies performed with some other strains of the same bacterium *viz*, *P. viridiflava* strain EB274 (California, USA) and EB227 (Israel) also

produced antifungal lipopeptides whose masses are identical to those of Ecomycins B and C. These compounds were able to inhibit the human pathogens *Cryptococcus neoformans* and *Candida albicans* as reported by Harrison *et al*.[48]

PSEUDOMYCINS

The Pseudomycins represent a group of peptide antifungal compounds isolated from liquid cultures of *Pseudomonas syringae,* a plant-associated bacterium. These antifungal peptide are also lipopeptides containing non traditional aminoacids like L-chlorothreonine, L-hydroxy aspartic acid and both D-and L-diaminobutyric acid. The *P. syringae* is a member of the Pseudomonadaceae family of Proteobacteria Phylum. Pseudomycin A, the predominant peptide in a family of four, pseudomycins A-D, has impressive activity against the human pathogen, *Candida albicans*.[48] Pseudomycins A-C contain hydroxyaspartic acid, serine, arginine, lysine and diaminobutyric acid. Pseudomycin D, on the other hand, has a molecular mass of 2401Da and is more complex than pseudomycins A-C. However, they are found to be different from the previously described antimycotics from *P. syringae,* including syringomycin, syringotoxin and syringostatins. They are effective against a variety of human and plant pathogenic fungi including *C. albicans* and *C. neoformans*.[48]

MUNUMBICINS

The Munumbicins represent a novel group of 4 bioactive substances. Munumbicins A, B, C and D are newly described antibiotics with a wide spectrum of activity against plant pathogenic fungi and bacteria, and a *Plasmodium* species. These compounds were obtained from a bacterium that has been deposited as *Streptomyces* NRRL 30562 in the mediPeoria USDA National Laboratory. It is an endophytic bacterium found in the Snake vine [*Kennedia nigriscans*], a medicinal plant native to the northern territory of Australia. The munumbicins act against Gram-positive bacteria such as *Bacillus anthracis, Streptococcus pneumoniae*, *Enterococcus faecalis* and *Staphylococcus aureus*.[49]Along with that, the methicillin-resistant strain of *S.aureus* (MRSA, ATCC 33591) and a vancomycin-resistant strain of *E. faecalis* (VREF, ATCC 51299) are two of the Gram-positive munumbicin-sensitive bacterial strains that are commonly drug-resistant. The munumbin B is effective against multiple-drug-resistant (MDR) *Mycobacterium tuberculosis*, an acid-fast bacterium. However, the most peculiar fact is that only the MDR strain of *M. tuberculosis* was sensitive to munumbin B whereas the drug-susceptible strain of this organism was less sensitive. The munumbicins C and D are of a special interest because in addition to being effective against Gram positive and negative bacteria, they are effective against the malarial parasite *Plasmodium falciparum*, the most pathogenic *Plasmodium* causing malaria. The munumbicin D was reported as more powerful than chloroquine, the gold-standard antimalarial drug.[50] Furthermore, munumbicins B, C and D did not cause any detectable lysis of human red blood cells. But these compounds were not effective against human pathogenic fungi. The munumbicins E-4 and E-5 were isolated from *Streptomyces* NRRL 30562. They are found to be effective against both gram-positive and gram-negative bacteria. The antimalarial activity of munumbicins E-4 and E-5 is reported to be double than that of chloroquine.[51]

KAKADUMYCINS

These are peptide antibiotics produced (in culture) by endophytic bacterium *Streptomyces* (NRRL30566) from a fern-leaved Grevillea tree [*Grevillea pteridifolia*, Synonym: *Grevillea chrysodendron* R.Br.] native to the northern territory of Australia.[52] Kakadumycin A is chemically related to echinomycin, another *Streptomyces* derived quinoxaline antibiotic, a potential anticancer drug.[53-54] Kakadumycin A, has antibacterial activity similar to Munumbicins; and it is also effective against *P. falciparum.*

XIAMYCINS

The Xiamycins represent one of the indolosesquiterpenes isolated from prokaryotes. They are novel pentacyclicindolosesquiterpene, named as Xiamycin-A and its methyl ester-2 obtained from *Streptomyces sp*. strain GT2002/1503, an endophyte from the mangrove plant, *Bruguiera gymnorrhiza.*[55] Interestingly, Xiamycin-A exhibits selective anti-HIV activity.[55] Three new indolosesquiterpenes, Xiamycin B (1b), Indosespene (2), and Sespenine (3), along with the known Xiamycin A (1a) from the culture broth of *Streptomyces sp*. strain HKI0595, a bacterial endophyte of the widespread mangrove tree, *Kandelia candel* has been reported by Ding *et al*.[56] Their research findings suggest that these Xiamycins do have moderate to strong antimicrobial activities against several bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*.

OTHER ANTIBIOTICS

From various tissues of medicinal plants, 78 EB has been reported by Jalgaonwala *et al*.[57] From these isolates, 15 EB do possess antifungal activity. They have also reported the strong antifungal activity of the bacterial isolates HB3 from rhizomes of *Curcuma longa*, KB4 from roots of *Pinus glabra*, and NB6 from stem *of Eucalyptus globulus*.[57]

The ability of EB to produce novel antibiotics and antimicrobial natural products has greatly fascinated scientist; and due to proven reported activities [Table 1], EB are viewed

Table 1: Novel antibiotics produced by endophytic bacteria and their reported activities

Name of the endophyte	Source of the endophyte	Chemical nature	Antibiotics isolated	Reported activities	Reference
Pseudomonas viridiflava EB 273	*Lactuca sativa*	Lipopeptides	Ecomycine B, C	Antifungal	[44]
Pseudomonas syringae	*Nicotiana benthamiana*	Lipopeptides	Pseudomycins A, B, C and D	Antifungal	[48]
Streptomyces sp. strain NRRL 30562	*Kennedia nigriscans*	Peptide	Munumbicin A, B, C and D	Gram positive and negative bacteria	[49], [51]
Streptomyces sp. strain NRRL 30566	*Greevillea pteridifolia*	Peptide with quinoxaline rings	Kakadumycin	Gram positive and negative bacteria	[52]
Streptomyces sp. GT 2002/1503	*Bruguiera gymnorrhiza*	Pentacyclicindolosesquiterpine	Xiamycin A	Anti HIV	[55]
Streptomyces sp. HK 10595	*Kennedelia candel*	Pentacyclicindolosesquiterpine	Xiamycin B, Indosespine and Sespenine	Antibacterial	[56]

as a promising potential source of novel antibiotics as well as a source of anticancer, antioxidant and immunosuppressive agents.

PERSPECTIVES

Endophytes are micro-organisms that are abundantly present in rainforest plants which occupy 7% of earth's land surface.[58] Due to huge diversity and untapped potential of EB, they appear as an alternate source of bioactive natural products with potential applications in pharmaceutical industry. Hence, EB have caught the attention of the pharmaceutical industry. However, EB as a source of new antibiotics against susceptible and resistant forms of micro-organisms is the most important and promising.

The development of resistance in microbes (especially pathogens) to most of the habitually used antibiotics keeps the search for new and novel antibiotics perpetual. For instance, some strains of *Mycobacterium* have developed resistance to many of the first line anti-tubercular drugs and a few second line anti-tubercular drugs leading to MDR and extensive drug resistant (XDR) *Tubercle bacilli* (TB). Therefore, the search for new drugs to deal with these resistant forms of TB has gained global attention. Much attention is being paid to the alternate sources of antibacterial agents against these resistant forms. Munumbicin B, an antibiotic from the endophytic bacterium is reported to be effective against MDR-TB. Further clinical trials with this compound may pave the way for an anti-MDR-TB drug.

Malaria (a protozoal infection) is very common in tropical countries. The gold standard anti-malarial agent chloroquin is associated with many fatal side-effects, for instance hemolysis. An agent (bioactive natural product/its derivative) devoid of these side-effects may be an added advantage in the treatment of malaria. Antibiotics like Munumbicin and Kakadumycins obtained from EB are reported to be effective against *P. falcipuram*, one of the causative organisms of malaria. Fixing these as the lead molecules, the search for anti-plasmodial drug, may yield an agent without the side-effects.

The MRSA and VREF represent the common resistant strains associated with hospital acquired infections. Presently few therapeutic options are available for the management of VREF[59] and MRSA.[60] Two of the antibiotics *viz*, Munumbicin and Xiamycins obtained from EB are proved to be effective against these resistant forms. Hence, future studies with such antibiotics in these infections may provide wider therapeutic options.

The fascinating fact is that some of these antibiotics (Ecomycins and Pseudomycins) are antifungal, especially against *Candida albicans* and *Cryptococcus neoformans*; whereas Xiamycins are anti-HIV in nature. It is well-known that the opportunist fungal infections in HIV patients are visceral candidiasis and cryptococcosis.[61] Thus a combination of Ecomycins and Xiamycins or Pseudomycins and Xiamycins may be additive and effective in HIV patients. However, the limitations of these combinations such as drug interactions and toxicity profile must be stringently monitored for the safety reasons. The elimination of these limitations may lead to invention of a new antiviral formulation. The EB which have multiple roles against many human pathogens may serve either an alternative or complimentary source of novel antibiotics in the future.

The International Union for Conservation of Nature and Natural Resources (IUCN) data suggest that there are 297,326 species of plants (including Monocotyledons, Dicotyledons, Gymnosperms, Ferns and allies, Mosses, Green Algae and Red Algae) [*Source*: http://www.

factmonster.com/ipka/A0934288.html]; and a very little number of species are studied for their endophytes. The EB do exist in virtually every plant on the earth.[33] Roots, nodules, stems, petioles, leaves, and flower tissues from each plant species of Monocotyledons (59,300 species), Dicotyledons (199,350 species), and Gymnosperms (980 species) can be used to isolate EB. Two to more than 16 species of EB can be isolated from different tissues of each plant species collected from relatively small area [our unpublished research data]. A large number of medicinal plants from all the countries are not studied for their endophytes; and we strongly believe that plant species with antimicrobial properties are likely to have endophytes that can produce novel antibiotics.

To sum up, the EB do have a huge potential in bioprospecting; and in the future, these EB are going to serve as one of the potential sources of novel antibiotics. For this reason, the current scenario warrants the expansive research to explore untapped, underutilized and neglected EB. However, an effective and efficient cross-talk amongst chemists, ethnobotanists, microbiologists, molecular biologists, pharmacists, taxonomists and toxicologists is essential in exploring EB for novel antibiotics and other natural products.

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