Siberian Plants : untapped repertoire of bioactive endosymbionts

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Abstract:

Endosymbionts are microbial plethora inhabiting all plant species and have been subject of interest among the scientific communities. These symbionts have gained tremendous interest in recent decades owing to their emerging biological roles. Plants inhabiting Siberian niches are one of the least studied among the plant diversity across the globe. Barcoding these plants can be interesting to reveal bioactive endosymbionts bearing myriad biological properties. With the globe being succumbing to various challenges like antimicrobial resistance, combating infectious diseases like HIV, tuberculosis, cancer and many genetic disorders. The microbial resource can address these challenges by secreting value added bioactive compounds bearing activities. Among the microbial consortium, one of the least targeted areas is endosymbionts which forms one of the superior repertoires of bioactive metabolites. Based on these facts and consideration, present review insights myriad roles of endosymbionts and makes the alarming call towards tapping Siberian plants for novel endosymbionts.

Keywords: Endosymbionts, Endophytes, Siberian Plants, Bioactive Metabolites, Novel compounds

1. Introduction

Plant as a sessile entity has enormously contributed towards the progress of mankind which can have been well documented in ancient records (Baker et al. 2013). Almost every living organism is directly or indirectly dependent on plants (Satish et al., 1999; Powledge 2011). The scientific interest in plants species led to revolutionize myriad Phyto-applications in different fields of science (Kavitha et al. 2013). One such scientific sector which has gained tremendous progress is plant based medicines. The pharmaceutical biology perceives plant as one of the inexhaustible sources of medicines which can cope the demand posed by the growing global population (Pan et al. 2011). However, not all efforts are successful owing to different drawbacks, for instance, slow growing rate, low yield, restriction to specific niches and harvesting of endangered species. Hence in recent times, scientific communities have expressed their interest beyond plant kingdom to reveal the role of plant associated micro-symbionts (Hale et al. 2014). Studies confer that plants harbor an untold number of microorganisms which are termed as epiphytes and endophytes or endosymbionts (Newman & Cragg 2015). Among which endophytic communities reside inside healthy living tissues of host plants. It has been reported that these microbial symbionts are capable of performing myriad biological functions ranging from plant protection, aid in phytoremediation, growth, and development (Turner et al. 2012). Ever since the word endophyte (endosymbiont) was introduced in the literature there has been burgeoning interest to reveal their myriad functionalities (Baker & Satish 2012). These microbial symbionts are reported to inhabit almost all plants species and have become the subject of interest to a large number of scientific studies (Syed et al. 2017). Sporadic scientific literature highlight these microbial symbionts mimic the host chemistry and are capable of secreting value added metabolite similar to its host plant. One of the classical examples of this phenomenon can be elucidated with the secretion of taxol from endosymbionts (Newman & Cragg 2015). There are different beneficial characteristics of endosymbionts which are being constantly explored (Fig. 1). The type of biological activity mainly depends on the host and its biological niches of the (Syed et al. 2015). Interestingly, plants form one of the rich living species which occupy different biological niches across the globe (Baker et al. 2015). One such biological niche includes the geographical area encompasses of the Siberian region which constitutes one of the vast region conquering almost northern Asia with its border extending through different countries like Russia, China, Kazakhstan, Mongolia and arctic regions (Raiklin 2008). Apart from its vast territory, varied climatic conditions, soil, and topography make Siberia one of the interesting habitat (Tchebakova et al. 2016). Till date, it can be believed that Siberia is one of the underexplored areas with scanty exploratory missions being carried out (Franke et al. 2004). The unique habitat of Siberian region harbors untold natural flora and fauna which upon exploration can be one of the natural warehouses of diverse biological entities. Since ancient era, the local Siberians are reported to explore the medicinal properties of plants in curing various ailments (Shikov et al. 2014). The traditional knowledge of these Siberian plants has been passed to generations with the keen observation of therapeutic effects and risk management. Most of these medicinal plants have been region specific and are yet to gain popularity at global scale. Based on these facts and considerations, present mini-review introduces the importance of Siberian plants and their untapped endosymbionts which can lead to tap the unique biological compounds bearing activity.

2. Siberian plants bearing activities

The emergence of life-threatening illness has continued to venture the globe and the situations are getting worse every time (Svidén et al. 2010), The limited choice of drugs has led to emergency situations in order to combat these ailments (Bertozzi et al. 2006). Medicinal plants thrive to be one of the vital sources of medicine with its constituents being used in most of the modern drugs (Newman & Cragg 2015). Use of plant-derived products can be traced since millennia (Satish et al. 1999). Even in the present times most of the plants extracts are used in order to prevent myriad human afflictions owing to their curative properties (Rather et al. 2016). Improved scientific knowledge and modern pharmaceuticals in past decades have demonstrated significant progress in industrializing plant-based therapeutic drugs (Baker et al. 2015). The large diversity of Siberian plants has continued to play curative agents till date with local Siberians practicing the plant-based formulations. The scientific inputs to these herbal based formulation is highly essential to barcode the biological entities responsible for activity. The floras of Siberian inhabitants are widespread with different biomes bearing rich diversity (Yashina et al. 2012). It may be estimated that over thousands Siberian plant species are known to be used in folk medicines and remains to be one of the most popular choice of drugs due to their immense potential in curing various ailments. Undoubtedly, these medicinal plants can act as excellent source of drugs but Siberian flora is one of the less explored areas with scanty exploratory missions being carried out till date. The systemic survey on rich floral resource on Siberian medicinal plants can open new horizons. Some of the studies have demonstrated biological properties of Siberian medicinal plants. For instance, *Bergenic crassifolia* (L.) is one of the popular folk medicine used in Siberia and other parts of the Asia (Popov et al. 2005). It constitutes different bioactive phyto-components bearing biological activities such as antimicrobial, antioxidants, Cerebro-protective, hepto-protective and adaptogenic (Kokoska et al. 2002). This plant is well-known with its common names like Siberian tea and Mongolian tea (Popov et al. 2005). Similarly, *Adonis vernalis* L. is also one of the popular folk medicine in different parts of Russia. In Siberia, *Adonis vernalis* L., is used in the treatment of heart and kidney disorders. Studies on *Adonis vernalis* L., reports the presence of flavonoids, phenolic compounds and cardenolides as the major components (Dragoeva et al. 2015). The Siberian flora, *Ledum palustre* L. is used as marsh tea which is said to have curative properties against arthrosis, cough-cold, leprosy, itches, bug bites and sore throats (Kim and Nam, 2006). The usage of *Atriplex halimus* is well-known owing to its medicinal properties in curing stomach pains, chest and intestinal aliments (Chikhi et al. 2014). *Atriplex halimus* considered to be vital source of vitamins, tannins, flavonoids, saponin, resins and alkaloids (Bayoumi et al., 1992). *Rhodiola rosea* is a medicinal plant inhabiting crevices of mountain rocks and sea cliffs in arctic region of Siberia (Marchev et al. 2016). It has long history of its traditional usage as medicine. The phyto-constitutes of this plants include sterol, essential oils, phenolic compounds, waxes, proteins and tannins (Panossian et al. 2010). The *Rhodiola rosea* reported to exhibit adaptogenic effects such as cardioprotective, neuroprotective, stimulating central nervous system, antidepressive, antifatigue and nootropic (Alm 2004). Similarly, the usage of *Rhaponticum carthamoides* is well documented in Siberian region with its adaptogenic properties (Lotocka and Geszprych, 2004). It is also used as diet supplement to promote muscle growth (Kokoska & Janovska 2009). The main constituents of *Rhaponticum carthamoides* are steroids and phenolic compounds (Opletal et al., 1997). The medicinal plant *Tussilago farfara* is one of the popular species among the local Siberian healers as it is widely used in treatment of cough and bronchial infections (Kokoska et al. 2002). The studies have also highlighted the antimicrobial, anti-inflammatory and antioxidative properties of *Tussilago farfara* (Xue et al. 2012). The *Bergenia crassifolia* is another plant species which is widely used as Siberian ethanomedicine. It possess antidiarrheal, anti-inflammatory and antimicrobial activities along with adaptogenic, immunostimulating and nootropic effects (Popov et al. 2005). *Chelidonium majus* L. is a medicinal herb which roots its traditional usages in wide range of pharmacological activities and used in treatment of oral infections, cancer, ulcers, bronchitis, asthma and many more (Maji & Banerji 2015). Studies have revealed that different parts of this plant contain wide range of phytocomponents such as chelidonine, berberine, sanguinarine and chelerythrine (Kokoska et al. 2002). The medicinal plant *Sanguisorba officinalis* used in treatment of hemostasis, inflammation and also possess antioxidant, anti-tumor, anti-HIV-1 and potent antimicrobial activities (Liang et al. 2013). Similarly, *Hedysarum theinum* is medicinal herb used in folk medicine of Siberian communities. It is reported to have anti-inflammatory, diuretic, pain-relieving source (Vdovitchenko et al. 2007). There are many plant species which are very popular among the local Siberian traditional healers and most of them are yet to be completely elucidated. Some of the risk associated with Siberian medicinal plants is their availability throughout the year. In most of the cases, owing to the harsh climatic conditions like abundant snowfall majority of these medicinal plants are destroyed and goes unused. The remaining few Siberian plants are reported to be endangered plant species and region specific which accounts for imbalance to plant diversity. Hence in order to cope with these critical issues, scientific communities have shifted their focus beyond the plant kingdom and recently isolating endosymbionts inhabiting medicinal plants has be subject of interest.

3. Different classes of endosymbionts

The term endosymbiont has broadened its definition based on its potential beneficial interaction with host (Partida-Martínez & Heil 2011). Virtually endosymbiont can be defined as microbial endo-assemblage or endo-inhabitant residing inside the healthy living tissues and forms imperceptible association with its host plants (Strobel & Daisy 2003). The first endosymbiont was described in Darnel which led to scientific interest for researchers to explore different endosymbionts (Kusari et al. 2012). The evidence of plant and its association with microorganisms has also been found with fossilized tissues of stems and leaves which clearly indicates that association evolved ever since the first plant appeared on earth (Schulz & Boyle 2006). Endosymbionts inhabit both monocotyledonous and dicotyledonous plants ranging from yews, oaks, pears to herbaceous plants such as maize, tomato, rice etc (Baker et al. 2015). The ideal characteristics of potent endosymbiont are illustrated in Fig. 2. Endosymbionts can be of different forms and majorly they may be grouped as fungal endosymbiont, bacterial endosymbionts and actinomycetic endosymbionts (Kusari et al. 2012). Till date, large number of scientific literature reported is pertaining to fungal endosymbionts. Further based on the source of its isolation, endosymbionts can be categorized as root endosymbionts, stem endosymbionts and leaves endosymbionts (You et al. 2012). According to Rodriguez et al., 2009, endosymbionts can be also classified as class1 endosymbionts which are reported to increase the host biomass and aid in drought tolerance and secrete chemicals which are toxic to animals, decrease the herbivory and prevent plants from being eaten. Similarly, Class II endosymbionts may be grouped based on their presence such as above and below ground level which indicates they are spatially distributed in different parts of the host plant and confer the habitat-specific stress tolerance to the host plant. Class III are distinguished based on their site of occurrence above the ground tissues and these types of endosymbionts are highly localized which includes hyperdiverse fungal endosymbionts and their endophytism with tropical trees, seedless vascular plants and conifers woody plants (Rodriguez et al. 2009).

4. Different protocols for endosymbionts isolation

Isolation of endosymbionts is one of the important process which is carried out under strict sterile conditions in order to eliminate the contaminants especially epiphytic flora (Kusari et al. 2012). Perusal of scientific literatures envisions different surface sterilization protocols which employ the use of combinatorial disinfectants and some of the majorly used are sodium hypochlorite, formaldehyde, mercuric chloride, ethanol, calcium hypochlorite and many more (Strobel & Daisy 2003). Further, the surface sterilization protocol is also coupled with the use of antibacterial and antifungal agents depending on the type of endosymbionts isolation (Baker & Satish 2012). For instance, in order to isolate bacterial and actinomycetic endosymbionts, use of antifungal agents like bavistin, cycloheximide are widely used in surface sterilization protocol or incorporated into media employed in isolation of endosymbionts (Baker & Satish 2015). These agents suppress the growth of fungal species and permit only bacterial endosymbionts to emerge out from the surface sterilized plants segments. Similarly, in order to isolate fungal endosymbionts, different antibacterial agents are used to inhibit the growth of bacteria which permits only emergence of fungal endosymbionts. Interestingly, use of microbiological medium for isolation also play vital role. The majority of studies highlights use of water agar for isolation of fungal endosymbionts and nutrient agar is also preferable for isolation of bacterial endosymbionts. Along with surface sterilization protocol and isolation media, there are several factors which influence the isolation of endosymbionts as described by Baker and Satish,2012. For instance, selection of plant species can also lead to influence the type of endosymbiont isolation. Plants with ethanopharmocological history will be interesting enough to isolate potent endosymbionts. As scientific literatures report that most of the endosymbionts are capable of mimicking host chemistry and are capable of secreting similar compound which are more active than the host (Kusari et al. 2012). The diversity of endosymbionts also depends on the biological niches where plant is inhabited and its geographical area (Baker et al. 2016b). The evidence of potent endosymbionts lodging in plants growing in rich biodiversity and unique habitats like harsh climatic conditions have been reported (Rodriguez et al. 2009). These physical factors not only influence the plants but also have greater impact on the endosymbionts present in plants (Kusar et al. 2012). Interestingly, type of plant parts selected also influence the endosymbiont isolation for instance endosymbionts isolated from the roots have influence of rhizosphere (Baker et al. 2016b). The selection of young plant tissues have been reported to be suitable for isolation of endosymbionts than the older tissues (Kusari et al. 2012).

5. Biological properties of endosymbionts

The importance of endosymbionts as rich source of bioactive metabolites can be exemplified with discovery of taxol, a billion dollar compound bearing anticancerous property (Strobel & Daisy 2003; Newman & Cragg 2015). Earlier, the sole source of taxol was yew tree and hence in order to isolate taxol and commercialize large number of yew trees were chopped off and taxol was marketed but endophytic research gave a new facelift with endosymbionts secreting taxol (Newman & Cragg 2015). These endosymbionts prevented further destruction of yew trees and taxol was produced via fermentation in large quantities. Apart from taxol there are myriad bioactive compounds secreted from potent endosymbionts which are brief discussed in the following section with respect to different biological activities. The secretion of antimicrobial metabolites from endosymbionts can be related to the independent evolution which can lead to incorporation of genetic information from host plants which in turn allow them to adapt inside the plants (Farrar et al. 2014).

5.1. Endosymbionts as source of Antimicrobial metabolites

The scientific studies envision endosymbionts as a rich source of antimicrobial agents with a large number of reports on isolation of antimicrobial metabolites (Baker et al. 2016b). The important antimicrobial agents isolated from endosymbionts includes naphtho-gamma-pyrones rubrofusarin B, asperpyrone B , aurasperone A and fonsecinone secreted from endosymbiont *Aspergillus niger* IFB-E003 inhabiting *Cyndon dactylon* (Ma et al. 2004). The endosymbiont *Chaetomium globosum* isolated from *Ginkgo biloba* secreted chaetomugilin D showed inhibitory activity against *Artemia salina* and *Mucor miehei* (Qin et al. 2009). The *Phoma sorghina* endosymbiont isolated from *Tithonia diversifolia* exhibited broad spectrum activity against all the test pathogens (Guimaraes et al. 2008). Similarly, p- amoniacetophenonic acids were purified from endophytic *Streptomyces griseus* isolated from *Kandelia candel* showed significant activity

(Guan et al. 2005). The derivatives of periconicins A and B purified from *Taxus cuspidate* endophytic fungus *Periconia* displayed antibacterial activity (Kim et al. 2004). *Cryptosporiopsis* species endosymbiont secreted cryptocandin which proved to be effective antifungal agents (Strobel et al. 1999). The cyclohexenine derivative ambuic acid was isolated from *Pestalotiopsis* and *Monochaetia* species associated with many tropical plants which efficiently suppressed the growth of test fungal pathogens thus forming potent antifungal agent (Li et al. 2001). The Coronamycin, a novel metabolite was isolated from endophytic *Streptomyces* species displayed antifungal activity against human fungal pathogens and anti malarial activity against *Plasmodium falciparum* (Strobel et al. 2004). Antiviral property with human cytomegalovirus protease inhibition was achieved with Cytonic acids A and B which was secreted by endophytic fungi *Cytonaema* species (Guo et al. 2000). Similarly, *Penicillium chrysogenum* isolated from Peru leaves displayed anti HIV-1 property by inhibiting integrase activity which is crucial for replication of HIV and the results were promising for developing new drug lead for anti-retroviral therapy (Singh et al. 2003). Interestingly, *Fusarium* species endosymbiont secreted fusaric acid which exhibited potent antimycobacterial activity against *M. bovis* BCG and *M. tuberculosis* H37Rv (Pan et al. 2011).Similarly, kakadumycin A and echinomycin metabolite purified from endosymbiont *Streptomyces* isolated from *Grevillea pteridifolia* displayed activity against Gram-positive bacteria and anti-malarial property against *Plasmodium falciparum* (Castillo et al. 2002).

5.2. Antidiabetic

As discussed earlier endosymbionts are reported to be one of the rich sources of novel leads bearing activities. One such activity includes antidiabetic, scientific studies have expressed the secondary metabolites secreted from endosymbionts are reported to profound antidiabetic activity. According to study conducted by (Dompeipen et al. 2011), 45 endosymbionts were screened for α glucosidase inhibitory activity from six medicinal plants of Indonesia. The results showed that seven endosymbionts were capable of expressing α glucosidase inhibitory activity. Similarly, seventeen fungal endosymbionts were isolated from *Salvadora oleoides* Decne which were further cultured and using different solvents crude extract was obtained which was tested for glucose tolerance test in glucose loaded fasting and alloxan induced diabetic *wistar albino* rats (Abhijeet Singh 2014). The results showed that four endophytic extract were reported to reduce the glucose levels. The compounds were purified to reveal its identity to 2, 6-di-tert-butyl-p-cresol and Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl (Dhankhar et al. 2013).

5.3. Anti cancerous

According to WHO, 80% of bioactive compounds are derived from natural resources like plants and microorganisms. In the case of finding new hopes for anticancerous agents, plants were considered to be one of the superior sources but indiscrimination and cutting down the plants can lead to loss of diversity especially endangered species. Recently it was revealed that endosymbionts act as an untapped source for anticancerous compounds. The first endosymbiont capable of secreting taxol, a potent anticancerous compound was isolated from *Taxomyces andreanae* (Stierle et al. 1995). Similarly, endophytic fungus *Entrophospora infrequens* isolated from *Nothapodytes foetida* was capable of secreting camptothecin a potent anticancerous compound (Amna et al. 2006). The study conducted by Kharwar et al. (2008), 183 endophytic fungi were isolated from *C. roseus* and screened for production of anticancerous compounds. The study revealed that *Alternaria* and *Fusarium oxysporum* were capable of secreting Vinca alkaloids bearing anticancerous activity. Further according to study conducted by Nadeem et al. (2012), reported that anticancerous compound podophyllotoxin was secreted from endophytic fungus *Fusarium solani* isolated from the roots of *Podophyllum hexandrum*. The endophytic fungus *Penicillium brasilianum* isolated from *Melia azedarach* was capable of secreting phenylpropanoids a potent anticancerous agent.

5.4. Anti inflammatory

Inflammation is a vital process for maintaining homeostasis. The available anti-inflammatory drugs are not so efficient and are bound with various side effects. Hence there is great demand for new and safe anti-inflammatory agents. Endosymbionts reported to be one such source which can secrete potent and ideal anti-inflammatory compound. Four different endosymbionts were isolated from *Loranthus* and screened for anti-inflammatory property. The results showed that *A.niger, Pencicillum* species and *Alternaria alternata* displayed anti-inflammatory property by inhabiting heat induced albumin denaturation and red blood cells membrane stabilization. Further proteinase activity was also inhibited and BSA HRBC stabilization assays indicated that extracts of endosymbionts possess anti-inflammatory properties (Govindappa et al. 2011). Similarly, ergoflavin, isolated from endophytic fungus inhabiting *Mimosops elengi* expressed significant anti-inflammatory activity (Deshmukh et al. 2009). Similarly, anticipated phloroglucinol present in the crude extract secreted from *Aspergillus fumigatus* displayed anti-inflammatory property (Karmakar et al. 2013).

5.5. Endosymbionts as source of biofuel

There has been serious concern for renewable energy sources. One such area gaining tremendous importance is biofuel from different natural resources. endosymbionts apart from its bioactive compounds, they are also capable of secreting compounds which bear potential for exploitation as biofuel. The endosymbiont *Gliocladium roseum* NRRL 50072 isolated from *Eucryphia cordifolia*, was capable of producing series of volatile hydrocarbons and their derivatives under microaerophillic conditions. The organism was capable of secreting alkanes, undecanes, heptanes, octanes and benzene (Stadler & Schulz 2009). Similarly, endosymbiont *Myrothecium inundatum* isolated from *Acalypha indica* L. was capable of producing a number of fuel related hydrocarbons like octane, 1,4-cyclohexadiene, 1-methyl-and cyclohexane upon growing in microaerophillic conditions (Banerjee et al. 2010).

5.6. Endosymbionts in agricultural sector

Agriculture is a backbone of any nation, it is estimated that owing to the pest attack a large number of agricultural products are being destroyed right from the period of sowing till the consumption of the product. There are several means to control these pest attack but a majority of prevention methods involve the use of hazardous elements in the form of pesticides and fungicides. These chemicals are bound to various limitations and are responsible for biomagnification and affect natural bodies and ecosystem. In recent studies, it was also estimated that penetration of pesticides into the human body and was detected in breast milk. Hence there is a serious concern regarding management of agriculture sector. In recent years, use of biological resources for biocontrol of pest has gained tremendous interest and plant associated microorganism are employed in the management of plant as these endosymbionts are reported to control the pest attack and also promote growth and development of host plants (Azevedo et al.

2000). These endosymbionts are responsible for triggering induced systemic resistance (ISR) which is very similar to that of systemic acquired resistance of plants. The studies also highlight that endosymbionts promote plant growth by cycling nutrient and minerals. They promote phosphate solubilization, indole acetic acid production, produces siderophores and also capable of supplying vitamins to host plants. These endosymbionts also attribute various beneficial processes like stomatal regulation, modification of root morphology and nitrogen metabolism. Recently, endosymbionts are also applied in the areas of forest regeneration and phytoremediation of contaminated soils

6. Future prospect of endosymbionts with respect to Siberian plants

The rich biodiversity of plants inhabiting Siberia is like a gold mine for endophytic research as scanty reports are available to best of our knowledge. Most of the plants are still be used among the Siberian local healers owing to its curative properties. Siberia being one of the biological niches with diverse geographical area and climatic conditions, availability of plants in all the seasons of the year is not possible and in order to isolate the compounds responsible for curative activity is always not possible as most of the plants are endangered species and harvesting them may results in loss of important flora and it may take decades to grow it again and some may not grow at all. Hence in order to address these implications, bar-coding of endosymbiotic microorganisms from Siberian plants will be promising enough to reveal the chemical diversity secreted from these symbionts. As these symbionts are reported to be chemical synthesizer inside the plants, evaluation of these endosymbionts can be very handy in reporting untapped microbial diversity which can lead to reporting novel endosymbionts which might be first of its kind. The present review makes an alarming call for the young researcher to take up Siberian plants and its associated endosymbionts as the subject of interest to tap the rich plant diversity. The success in barcoding the endophytic plethora bearing activity is only possible with association and collaboration of different expertise coming under one roof and working in hunt for potent endosymbionts.

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Figure 1 Endophytes (Endosymbionts) and their biological properties

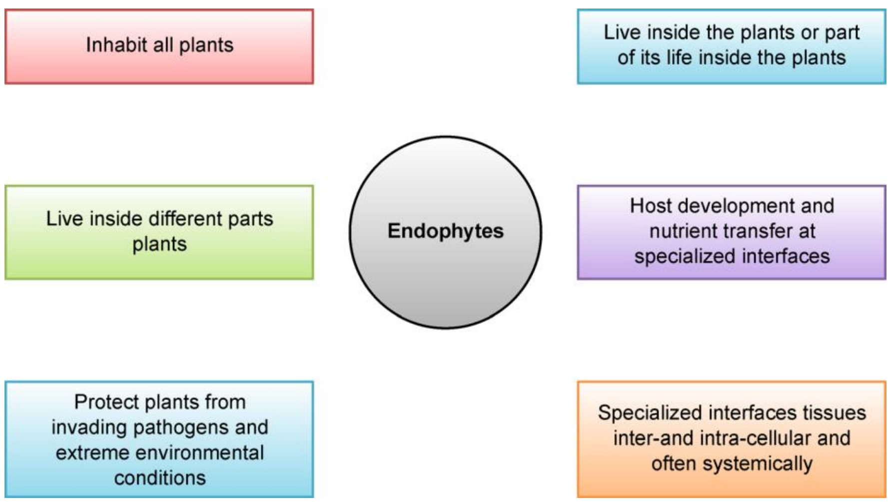

Figure 2 Characteristics of endophytes (endosymbionts).

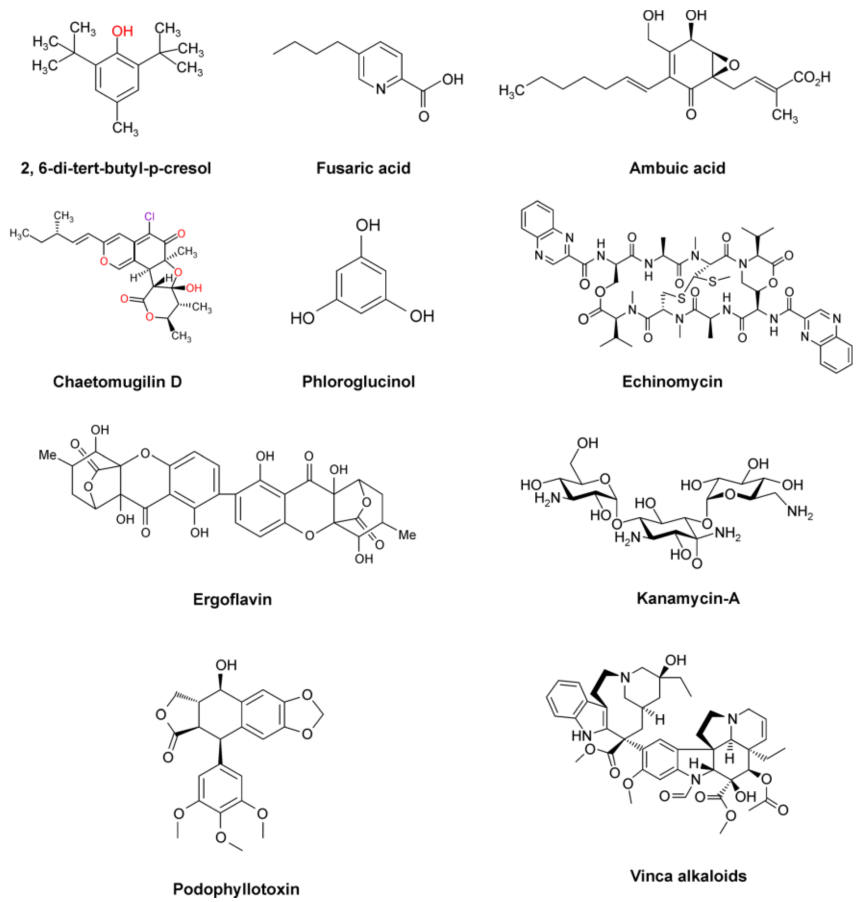

Figure 3 Important Secondary metabolites secreted from endosymbionts

Table 1 Bioactive metabolites secreted from endosymbionts bearing biological potential

Endosymbionts	Host	Bioactive metabolite	Activity	References
Pseudomonas viridiflava	Grass	Ecomycins B & C	Antimicrobial	Miller et al., 1998
Chaetomium globosum	*Ginkgo biloba*	Chaetoglobosins A & C	Antimicrobial	Qin et al., 2009
Periconia sp.	*Taxus cuspidate*	Periconicins A & B	Antibacterial	Kim et al., 2004
Guignardia sp.	*Spondias mombin*	Guignardic acid	Antibacterial	Rodrigues-Heerklotz et al., 2001
Botryosphaeria rhodina	*Bidens pilosa*	Botryorhodines A-D	Antifungal	Randa et al., 2010
Streptomyces sp.	Monstera sp.	Coronamycin	Antifungal	Ezra et al., 2004
Cytonaema sp.	*Quercus* sp.	Cytonic acids A	Antiviral	Guo et al., 2000
Streptomyces NRRL 30562	*Kennedia nigriscans*	Munumbicin D	Anti malarial	Castillo et al., 2002
Streptomyces sp.	*Bruguiera Gymnorrhiza*	*Xiamycin*	Anti-HIV	Ding et al., 2010
Aspergillus niger. IFB-E003	*Cyndon dactylon*	Rubrofusarin B	Anti-tumor	Song et al., 2004