Current Understanding of Bacterial Endophytes as an Enriched Source of Antibacterial Compounds

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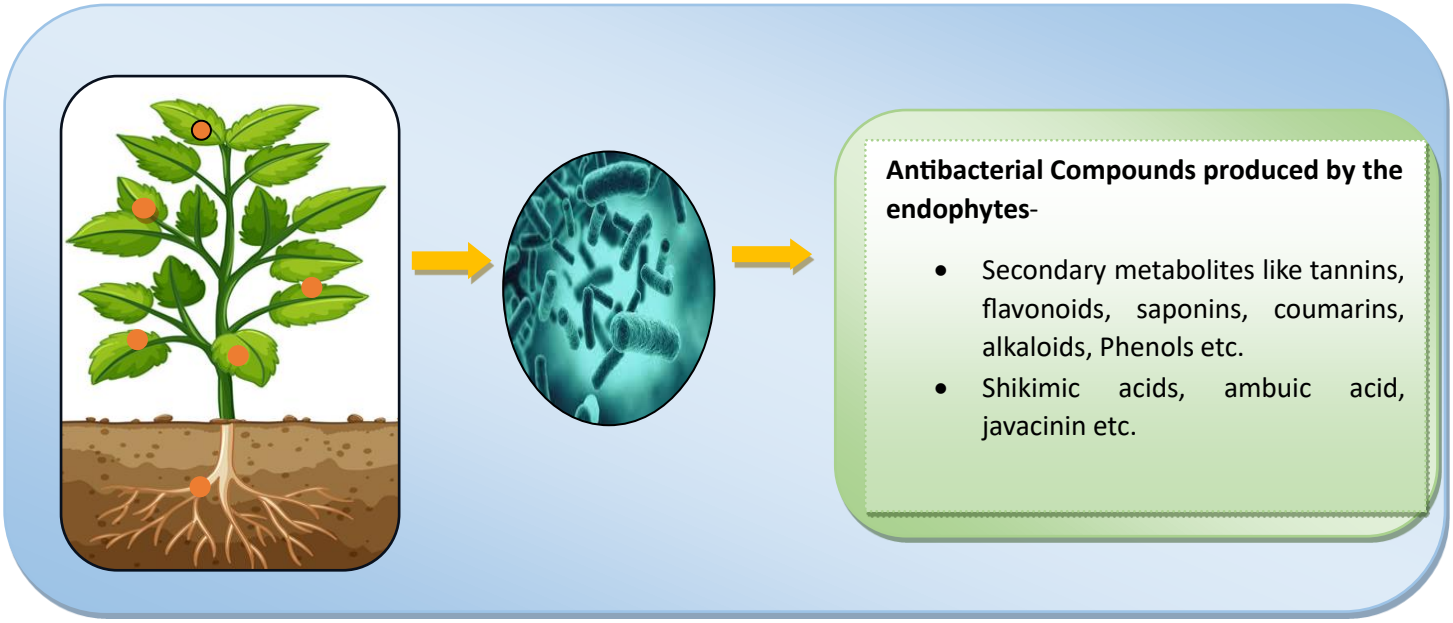
Abstract:

An exponential increase in population growth along with the alarming rise in bacterial infections invokes the need to find antimicrobial agents to tackle public health issues. Research to discover novel antibiotics against drug-resistant bacteria has become pivotal, especially after the emergence of the coronavirus pandemic. Various studies have shown that endophytic bacteria and fungi are found to synthesize various antibacterial compounds and secondary metabolites that can be treated against many resistant pathogenic microorganisms. The innocuous colonization of the endophytic bacteria inside the host and their ability to synthesize various beneficial compounds has led to various research to exploit them for medicinal applications. This review aims to highlight the importance of endophytes as a source of antibacterial agents against bacteria of medical importance.

I. Introduction:

Nature is a repository of abundant sources of novel drugs that are yet to be identified with therapeutic properties. Post the pandemic era there has been an exponential increase in the field of research which even led the scientific world to explore the realm of plants to develop a quick cure. After the Covid- 19 researchers have advanced in the field of omics to identify potential plant-derived molecules for drug discovery (Chojnacka et al. 2020). Various studies have been conducted to search for plant-derived polyphenols whose extracts are potent agents in coronavirus treatment and prevention (Singh et al. 2021). In the current review, we explore the potentiality of plant microbes, especially that of endophytic bacteria whose compounds might be potent antimicrobial agents that might help plants fight pathogenic microorganisms. Various reports prove that most of the plants studied to date have the presence of a myriad of endophytes thus proving the multifaceted relation between the host and microbe (Gouda et al. 2016). Endophytes are plant-colonizing microorganisms that inhabit the internal tissues without causing any harm to the host (Kandel et al. 2017). The multifaceted relationship between the endophytes and the host has proved to be advantageous as most of them produce valuable compounds which have antimicrobial, antioxidant or antitumor properties (Wang et al.2014, Palem et al. 2015 Pan et al.2017). The endophytes produce various secondary metabolites that have antagonistic activity thereby defending the host from another pathogenic invasion (Shukla et al. 2014; Godstime et al. 2014)

Fig1: Endophytes a rich source of antibacterial Compounds:



II. Endophytes- A source of Antibacterial Compounds:

Secondary metabolites play a pivotal role as defensive compounds that safeguard plants against pathogenic attacks (Divekar et al.2022). Various favourable factors like ease of isolation, growth and minimal side effects on the environment have ameliorated microbes to be good sources of extraction for biologically active compounds that could have antimicrobial activity (Cowman 1999). Many plant secondary metabolites possess antimicrobial activity which includes phenolics and polyphenols, flavonoids, quinones, tannins, coumarins, terpenoids, diterpenoids, alkaloids, lectins, polypeptides, polyketides and anthraquinones. (Savoia et al.2012, Upadhyay et al. 2014, Compean et al. 2013, Zheng et al.2021).Various studies have reported the presence of azadirachtin in endophytic bacteria (Kharwar et al.2008).Over the years, it has been found that plants do not live independently but have co-evolved gradually with the microorganisms forming a consortium. This plant microbiome plays a significant role in plant productivity, health and survival through the production of various antimicrobial compounds (Raaijmakers et al.2012). In most cases, the majority of the compounds have antimicrobial properties and it is estimated that these properties include protection of the host plant from various pathogens, like bacteria, viruses, fungi, nematodes, etc. (Gunatilaka et al. 2006). The endophyte-host consortium has enabled most of the endophytic bacteria, fungi and actinomycetes to play a significant role in the production of bioactive compounds. Recent reports show that various endophytes produce plant-derived secondary metabolites like terpenoids, alkaloids, polyketides, non-ribosomal peptides (NRPs), phenols, enzymes, & phytohormones that have the potential to cure SARS-COV 2. (Akter et al. 2022).

III. Antibacterial Compounds from Endophytic Fungus:

Singh et al. (2023) summarized the isolation, characterization, and role of secondary metabolites isolated from fungal endophytes and their pharmaceutical application. Their article shed light on the production of secondary metabolites from endophytic fungus, high throughput methods for analysis, and their pharmaceutical application. Studies showed that the endophyte *Alternaria* spp. showed antibacterial activity against various pathogens and a novel alkaloid altersetin was isolated from the endophyte Fadiji et al. (2020) isolated fungal endophytes from *Artemisia annua* which have the ability to inhibit most phytopathogenic organisms due to the occurrence of n-butanol and ethyl acetate. The studies put forward by Stierle et al. (1993) identified the diterpenoid alkaloid taxol which was the first secondary metabolite that was isolated from the endophytic fungus *Taxomyces andreanae* from the bark of *Taxus brevifolia* Following this various studies have been conducted to identify the use of secondary metabolites of endophytic origin as alternate eco-friendly sources of antimicrobial compounds. Sharma et al. (2016) isolated *Pestalotiopsis neglecta* BAB-5510, an endophytic fungus from *Cupressus torulosa,* which was found to be a rich source of phenols, flavonoids, terpenoids, alkaloids, tannins, carbohydrates and saponin Reports put forward that crude extracts of endophytic fungus *Pestalotiopsis pro*duced Six novel ambuic acid derivatives and a new torreyanic acid analogue which had the capability to inhabit the lichen *Multiclavula* sp. (Ding et al.2009). Chen et al. (2016)concluded through their studies that volatile oils such as β-caryophyllene, zingiberene, caryophyllene oxide, β-sesquiphellandrene, hinesol, β-eudesmol and atractylon were produced from *Atractylodes lancea* due to the close association of the endophytic fungus *Gilmaniella* sp. AL12 with the host plant. The endophyte *Trichoderma ovalisporum* strain PRE-5 of the root of the herbal *Panax notoginseng* was found to produce Shikimic acid and was found to show activity against *S. aureus*, *Bacillus cereus*, *M. luteus* and *E. coli*. (Dang et al.2010). Bioactive compounds like Cycloepoxylactone and cycloepoxytriol were derived from the endophytic fungus *Phomopsis* sp. (internal strain no. 7233) of *Laurus azorica* which showed moderate antibacterial activity against *B. megaterium.* (Hussain et al. 2009 a). The endophytic fungus *Aspergillus sp. EJC08,* was reported to be isolated from the medical plant *Bauhinia guianensis* . Results showed the presence of the alkaloids, Fumigaclavine C and Pseurotin A . Both Fumigaclavine C and Pseurotin A expressed antibacterial activity against *B. subtilis, E. coli, P. aeruginosa, and S. aureus*. (Pinheiro et al. 2013) The bioactive compound Sclerotiorin was isolated from the endophyte *Penicillium sclerotiorum* PSU-A13 which was reported to have antibacterial activity against *S. aureus* ATCC 29213 (MIC 128 μg/mL) (Lucas et al. 2007; Arunpanichlert et al. 2010). Satisfactory antibacterial activity was reported from the endophytic fungus *Cytospora* sp. CR200 isolated from *Conocarpus erecta* . Reports conclude that the activity shown by the endophyte was due to the presence of Cytosporone D, E, and Cytoskyrin A. Singh et al. (2007). Various endophytic fungi isolated from different types of plants across the world were summarized (Deshmukh et al. 2015). Liu et al. (2008) reported the presence of the bioactive compound 7-amino- 4-methylcoumarin from the extracts of the endophytic fungus *Xylaria sp.* YX-28 isolated from *Ginkgo biloba* L. They started the existence of antibacterial activity against food spoilage microorganisms such

as *Staphylococcus aureus, Escherechia coli, S. typhia, S. typhimurium, S. enteritidis, A. hydrophila, Yersinia sp., V. anguillarum, Shigella sp., V. parahaemolyticus, C. albicans, P. expansum, and A. niger.*

Table 1: List of few bioactive compounds isolated from endophytic fungi that shows antibacterial activity.

S.No.	Name of the host plants	Name of the endophytic fungi	Chemical compound Reported / Secondary metabolite	Reference
1.	*Azadirachta indica* A. Juss	*Chloridium* sp.	Javanicin	Kharwar et al. 2008
2.	*Ginkgo biloba*	*Xylaria* sp. YX28	7-amino-4-Methylcoumarin	Liu et al. 2008
3.	*Plumeria acutifolia*	*Phomopsis* sp.	Terpenoid	Nithya et al. 2010
4.	*Lichen Clavaroids*	*Pestalotiopsis* sp.	Ambuic Acid Ambuic acid derivative	Ding et al.,2009
5.	*Cupressus torulosa*	*Pestalotiopsis neglecta* BAB-5510	Phenols, flavonoids, terpenoids	Sharma et al.2016
6.	*Atractylodes lancea*	*Gilmaniella* sp. AL12	β-caryophyllene, zingiberene, caryophyllene oxide, β-sesquiphellandrene, hinesol, β-eudesmol	Chen et al. 2016
7.	*Panax notoginseng*	*Trichoderma ovalisporum* strain *PRE-5*	Shikimic acid	Dang et al. 2010
8.	*Laurus azorica*	*Phomopsis* sp. (internal strain no. 7233)	Cycloepoxylactone and cycloepoxytriol	Hussain et al.2009a
9.	*Bauhinia guianensis* .	*Aspergillus sp. EJC08,*	Alkaloids, Fumigaclavine C Pseurotin A	Pinheiro et al. 2013
10.	-	*Penicillium sclerotiorum PSU-A13*	Sclerotiorin	Lucas et al. 2007; Arunpanichlert et al. 2010
11	*Conocarpus erecta* .	*Cytospora sp. CR200*	Cytosporone D , E , and Cytoskyrin A	Singh et al. 2007
12.	*Ginkgo biloba*	*Xylaria sp. YX-28*	7-amino- 4-methylcoumarin	Liu et al.2008

IV. Antibacterial Compounds from Endophytic Bacteria:

Sing et al.(2017) were able to successfully prove the antibacterial activity of Silver nanoparticles(AgNPs) tested against human pathogens and observed that the AgNPs exhibited relatively high antibacterial activity against Gram-positive and Gram-negative bacteria. It was reported that the extracts of *Coniothyrium sp*. isolated from the rhizomes of *Aralia nudicaulis*, contains palitantin, botrallin, craterellin C, mycosporulone, spiromassaritone, and massarigenin D thus exhibiting antibacterial activity (Li et al. 2015). Efomycin, Efomycin G, Oxohygrolidin, Abierixin and 29-O-methylabierixin were identified from endophytic isolates of *Streptomyces sp. BCC72023* from *Oryza sativa* (Supong et al. 2016).*Streptomyces sp. BO-07* was identified from *Boesenbergia rotunda (L.)* Mansf A. Igarashi et al.(2004) stated that the bioactive compound Coumarin from *Streptomyces sp. TP-A0556* isolated from *Aucuba Japonica* had antibacterial activity against several pathogens. Miller et al.(1998) mentioned the presence of *Pseudomonas viridiflava from Grass* and they concluded that the antibacterial activity showed by the isolates was due to the presence of Ecomycins B and C. Menpara et al. (2013) summarized data on endophytic bacteria isolated from different plants and the secondary metabolites produced by these endophytes with antimicrobial activity against plant and human pathogenic bacteria.

Table 2: List of endophytes and their bioactive compounds isolated from endophytic Bacteria.

S.No.	Name of the host plants	Name of the endophytic bacteria	Chemical compound Reported / Secondary metabolite	Reference
1.	*Oryza sativa* L**.**	*Streptomyces sp. BCC72023*	Efomycin Efomycin G Oxohygrolidin Abierixin 29-O-methylabierixin	Supong et al. 2016
2.	Grass	*Pseudomonas viridiflava*	Ecomycins B and C	Miller et al.1998
3.	Boesenbergia rotunda (L.) Mansf A	*Streptomyces sp. BO-07*	3′-hydroxy-5-methoxy-3,4-methylenedioxybiphenyl	Taechowisan et al. 2017
4.	*Aucuba Japonica*	*Streptomyces sp. TP-A0556*	Coumarins	Igarashi et al. 2004

5.	*Mahonia fortunei*	*Bacillus wiedmannii*	ergosterol derivative, 23*R*-hydroxy-(20*Z*,24*R*)-ergosta-4,6,8(14),20(22)-tetraen-3-one	Wang et al. 2019
6.	*Tridax procumbens* L	*B. amyloliquefaciens, B. indicus, B. pumilus, B. subtilis).*	Flavonoids, Saponins	Praveena et al. 2013
7.	*Calotropis procera*	*Bacillus siamensis*	Tannins, flavonoids, saponins, and phenolics	Hagaggai et al. 2020

V. Conclusion and future perspectives:

The alarming rise in the number of infections caused by drug-resistant pathogens has made scientists across the world explore novel antibiotics and their bioactive compounds at a fast pace so as to i) curb infections caused by drug-resistant bacteria ii) Increase occurrence of novel diseases caused by microorganisms ii) appearance of SARS- COVID -2 iii) widespread of several infectious diseases and the high mortality rate caused by infectious diseases like NIPAH and COVID 2 iv) Reappearance of infectious diseases and v) Unavailability of microorganisms targeted drug. Endophytes are a new area of the plant-microbe world that has been recently explored because of: a) synthesis of various bioactive compounds and secondary metabolites which can be harnessed to produce novel drugs b) New drug targets can be explored due to the resistant varieties that are being identified c) Fast growth rate d) Easy mode of culturing and studying e) Availability of nutrients f) better antibacterial and antibiotic sensitivity than plants g) Symbiotic and beneficial relation with plants h) They cause no or less side effects to the environment. The present review summarizes the various antibacterial compounds hidden in various endophytes and their association with different plants. This proves that endophytes are an area that can be still explored to harness these antibacterial compounds to develop novel drugs to treat various diseases across the world.

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