CURRENT UNDERSTANDING OF BACTERIAL ENDOPHYTES AS AN ENRICHED SOURCE OF ANTIBACTERIAL COMPOUNDS

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. Previous reports have proved that several endophytic bacteria and fungi are found to produce 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 researches to exploit them for medicinal applications. This review was compiled with the aim of focusing on the importance of endophytes as a source of antibacterial agent against other pathogens; thus exploring the hidden realm of endophytes as a potent source in the field of medicine.

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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 area of research which made 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). Several researches have been conducted to analyse the 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 duos (Gouda et al. 2016). Endophytes are plant-colonizing beneficial microbes that colonize in the tissues of the host without causing much impairment and thereby playing a pivotal role in the overall growth of the plant (Kandel et al. 2017). This multifaceted association host has been demonstrated 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 yield various bioactive compounds that have antagonistic activity thereby defending the host from any other pathogenic invasion (Godstime et al. 2014; Shukla et al. 2014).

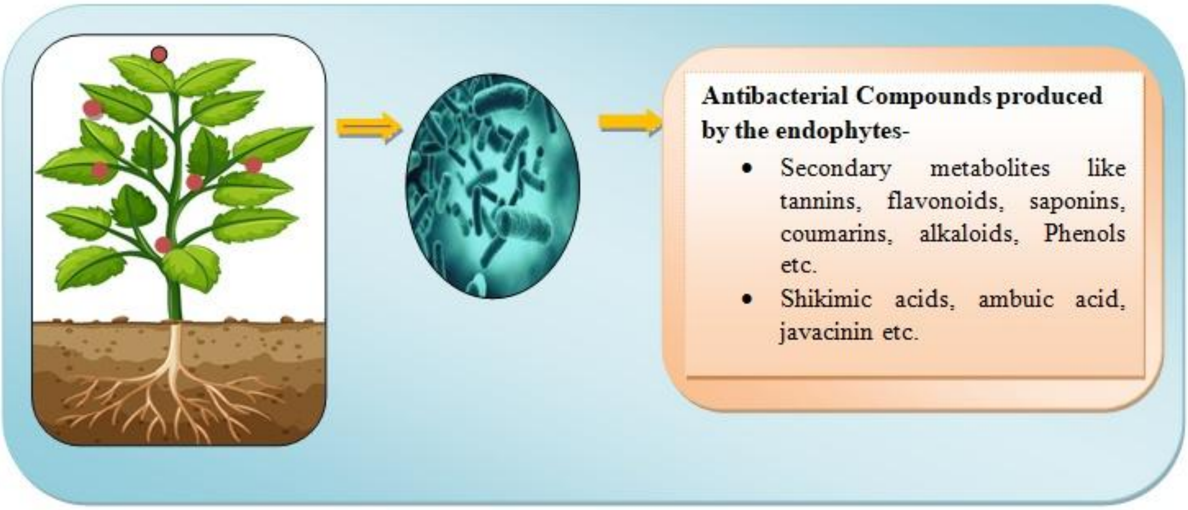

Figure 1: Endophytes a Myriad Source of Antibacterial Compounds

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 phenolic and polyphenolic compounds, flavonoids, quinones, tannins, coumarins, terpenoids, diterpenoids, alkaloids, lectins, polypeptides, polyketides and anthraquinones. (Compean et al. 2013; Savoia et al. 2012, Upadhyay et al. 2014, Zheng et al.2021).Various scientists have stated 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 as a protagonist in plant productivity, overall health and existence of the host through the synthesis of several antimicrobial compounds (Raaijmakers et al. 2012). While exploring the realm of endophytes various scientists like Gunatilaka et al. (2006) explored that several compounds synthesized by the endophytes have antimicrobial properties and it has been appraised that these properties play a dominant role in the defending host plant from various pathogens like viruses, bacteria, fungi, nematodes, etc. The endophyte-host consortium has empowered most of the endophytes (bacteria, fungi & actinomycetes) to perform a substantial protagonist in the production of bioactive compounds. Akter et al. 2022 worked on several medicinal plants to identify the potential endophytes that could produce plant-derived bioactive compounds which can be potent agents for drug innovation to cure SARS-COV-2.

III. ANTIBACTERIAL COMPOUNDS FROM ENDOPHYTIC FUNGUS

In 2023, Singh et al. described in his review the presence of secondary metabolites from fungal endophytes and their ability to be exploited for novel drug production. Fadiji et al in 2020 reported that the isolate *Alternaria* spp. which was endophytic in nature showed satisfactory antibacterial activity counter to various pathogens and further studies on the isolate led to the discovery of a novel alkaloid Altersetin. They also reported the occurrence of fungal endophytes from *Artemisia annua* which was able to obstruct the growth of several phytopathogenic organisms due to the occurrence of n-butanol and ethyl acetate. The studies put forward by Stierle et al. (1993) recognized the first secondary metabolite Taxol a diterpenoid alkaloid that was isolated from the endophytic fungus *Taxomyces andreanae* from the bark of *Taxus brevifolia*. Following these various studies have been steered to identify and to exploit the secondary metabolites produced by the endophytes as an alternate eco-friendly source of antibacterial compounds. Sharma et al. in (2016) isolated the endophyte *Pestalotiopsis neglecta* BAB-5510 from the gymnosperm *Cupressus torulosa*, which was found as a rich source of several metabolites like flavonoids, terpenoids, phenols, tannins, alkaloids, carbohydrates and saponin. Reports put forward that the crude extracts of the endophytic fungus *Pestalotiopsis* produced six novel compound ambuic acid derivatives and a new torreyanic acid analogue which was found to have the potentiality to inhabit the lichen *Multiclavula* sp. (Ding et al. 2009). Chen et al. (2016) reported the presence of several compounds such as caryophyllene oxide, β-caryophyllene, β-sesquiphellandrene, zingiberene, hinesol, β-eudesmol and atractylon and they concluded that these volatile compounds played a very significant role in antibacterial activity which was due to the symbiotic association of the endophytic *Gilmaniella* sp. AL12 with *Atractylodes lancea.* Studies were conducted on the roots of *Panax notoginseng* which showed the presence of the endophyte *Trichoderma ovalisporum* strain PRE-5 and shikimic acid produced by the isolate expressed antibacterial activity against *Bacillus cereus*, *M. luteus*, *S. aureus* and *E. coli*. (Dang et al. 2010). Satisfactory antibacterial activity was exhibited by the endophyte *Phomopsis* sp. (internal strain no. 7233) isolated from *Laurus azorica* against the bacterial strain *B. megaterium.* It was reported that this activity was due to the production of bioactive compounds like Cycloepoxylactone and cycloepoxytriol that were derived from the endophyte. (Hussain et al. 2009 a). Pinheiro et al. in 2013 isolated the endophyte *Aspergillus sp.* EJC08 from the *Bauhinia guianensis.* Their results exhibited that the fungal endophyte produced several alkaloids like Pseurotin A and Fumigaclavine C that were found to show antibacterial activity against, *E. coli, B. subtilis, P. aeruginosa, and S. aureus*. (Pinheiro et al. 2013) The bioactive compound Sclerotiorin showed moderate results for antibacterial activity against *S. aureus* ATCC 29213 which was due to the close association of the endophyte *Penicillium sclerotiorum* PSU-A13 with the host plant. (Arunpanichlert et al. 2010; Lucas et al. 2007). 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 , and Cytoskyrin A, Cytosporone D & Cytosporone E. Singh et al. (2007). Deshmukh et al. in 2015 summarized the data of huge plethora of endophytic fungus that were isolated from different plants across the world.The occurrence of several compounds like 7-amino- 4-methylcoumarin were recognized when studies were conducted with the extracts of the endophyte *Xylaria sp.* YX-28 isolated from G*inkgo biloba* L as reported by Liu et al in 2008. Through their study they were able to prove that these endophytes were potent antibacterial agents against food spoilage pathogens such as *Escherechia coli, A. hydrophila, S. typhia, S. enteritidis, S. typhimurium Yersinia sp., V. anguillarum, Shigella sp., Staphylococcus aureus, C. albicans, V. parahaemolyticus, P. expansum, and A. niger* which were associated with the compounds synthesised by the endophytes. Studies with several endophytes have proved to produce chemical compounds that showed antibacterial activity as summarized in Table 1 and Table 2.

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

S.No.	Name of the Host Plants	Endophytic Fungi Isolated	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	Flavonoids, terpenoids, Phenols	Sharma et al.2016
6.	*Atractylodes lancea*	*Gilmaniella* sp. AL12	β-caryophyllene, β-sesquiphellandrene zingiberene, β-eudesmol caryophyllene oxide, hinesol,	Chen et al. 2016
7.	*Panax notoginseng*	*Trichoderma ovalisporum* strain	Shikimic acid	Dang et al. 2010

		PRE-5		
8.	*Laurus azorica*	Phomopsis sp. (internal strain no. 7233)	Cycloepoxytriol, Cycloepoxylactone	Hussain et al.2009a
9.	*Bauhinia guianensis* .	Aspergillus sp. EJC08,	Alkaloids, Pseurotin A & Fumigaclavine C	Pinheiro et al. 2013
10.	-	Penicillium sclerotiorum PSU-A13	Sclerotiorin	Arunpanichlert et al. 2010 Lucas et al. 2007
11	*Conocarpus erecta* .	Cytospora sp. CR200	Cytosporone D, Cytosporone E & 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 proved the presence of antibacterial activity of silver nanoparticles (AgNPs) tested against human pathogens and deduced that the high antibacterial activity against bacteria was due to AgNPs produced by the endophytes. It was reported that the extracts of *Coniothyrium sp*. isolated from the rhizomes of *Aralia nudicaulis* showed the presence of botrallin, palitantin, mycosporulone, craterellin C, spiromassaritone, and massarigenin D thus exhibiting antibacterial activity (Li et al. 2015). Efomycin G, Oxohygrolidin, Efomycin, 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 *Streptomyces sp. TP-A0556* isolated from *Aucuba Japonica* exhibited the presence of the bioactive compound Coumarin which showed 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 endophytes which showed effective antimicrobial activity against human pathogenic bacteria and plant.

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, 29-O-methylabierixin, Efomycin G, Oxohygrolidin, Abierixin	Supong et al. 2016
2.	Grass	*Pseudomonas viridiflava*	Ecomycins B and C	Miller et al.1998
3.	*Boesenbergia rotunda* (L.)	*Streptomyces* sp. BO-07	4methylenedioxybiphenyl, 3′-hydroxy-5-methoxy-3	Taechowisan et al. 2017
4.	*Aucuba japonica*	*Streptomyces* sp. TP-A0556	Coumarins	Igarashi et al. 2004
5.	*Mahonia fortunei*	*Bacillus wiedmannii*	ergosterol derivative, 23R-hydroxy-(20Z,24R)-ergosta-4,6,8(14),20(22)-tetraen-3-one	Wang et al. 2019
6.	*Tridax procumbens* L	*B. indicus, B.amyloliquefaciens, B. pumilus, B.subtilis).*	Saponins, Flavonoids	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 triggered 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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