Endophytic Bacteria and Fungi from Indonesian Medicinal Plants with Antibacterial, Pathogenic Antifungal and Extracellular Enzymes Activities: A Review

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Abstract.
The habitat of endophytic bacteria and fungi in plant tissues makes it automatically used by plants to protect themselves against pathogenic microorganisms. Endophytic bacteria and fungi have been applied in various fields, including agriculture, pharmacy, medicine, and biotechnology. This review was carried out to summarize recent studies focusing on the diversity of endophytic bacteria derived from traditional medicinal plants that have antibacterial activity and extracellular enzymes. This review article was prepared and written by referring to literature studies collected from online journal publications of endophytic bacteria focused on Vernonia anthelmintic, Saurauia scaberrinae, and Ki rinyuh (Chromolaena odorata) plants. The results revealed that endophytic bacteria obtained from Vernonia anthelmintic plant belong to the bacterial genera Micrococcus, Bacillus, Pseudomonas, Stenotrophomonas, and Pantoea which possess the same biological properties as the host plant, producing antibacterial activity. The Saurauia scaberrinae plant successfully isolated endophyte fungus Phoma sp. which produces phomodione (4) and cercosporamide. Phomodione (4) exhibit inhibitory activity against S. aureus, P. ultimum, S. sclerotiorum and R. solani. Cercosporamide exhibits inhibitory activity against S. aureus. Endophytic bacteria were isolated from Ki rinyuh, including BECB3, BECB 4, BECA 8, BECA 5, BECA 1, and BECA 10 isolates which have extracellular enzyme activities such as β-amylase, α-amylase, cellulase, chitinase, and protease. Understanding endophytic bacteria in medicinal plants can help researchers them effectively as a biotechnological product.

Keywords: *Endophytic bacteria, medicinal plants, antibacterial, extracellular enzymes*

I. INTRODUCTION

Research on endophytic bacteria and fungi derived from medicinal plant organs in past decades is continuously indicating an escalation graph. Such increase was affected by the scientists' movement to find bioactive compounds of endophytic bacteria and fungi that are similar to their host plant compounds. Furthermore, the term 'endophyte' should be noted as the name proposed by Heinrich Anton de Bary in 1866 which was taken from the Greek words *endon* (inside) and *phyte* (plant) [1].

Endophytes are generally related to nonpathogenic bacteria and fungi inhabiting plant tissues, but are sometimes also used to refer to mycorrhizae found in plant roots. The positive effects due to the presence of endophytes for the plants include increasing the health, size, and continuity of plant growth. Endophytic bacteria and fungi are currently categorized as potential sources of new natural products for their exploitation in the fields of medicine, agriculture, and industry. Endophytic bacteria isolated from traditional medicinal plants have been reported to produce antibacterial, antifungal, and antiseptic compounds [2,3]. Furthermore, the secondary metabolites from endophytic fungal cultures have been previously proven to have cytotoxic, antimicrobial, antiviral, and anticancer activities [4,5,6,7,8,9,10,11,12]. In addition, plants that have significant biological activity have the potential to hide endophytes with the same bioactivity [11,13]. In this case, for example, endophytic bacteria isolated from medicinal plants of *Solanum distichum, Matricaria chamomilla, Calendula officinalis* [14], and *Hypericum perforatum* [15] showed excellent antibacterial and antifungal activity.

In addition, endophytic fungi isolated from leaves of the endemic plant of *Zygophyllum Mandeville*, which is *Cladosporium Cladosporioides*, has the best antimicrobial activity causing an inhibition ranging from 20.7 to 25.7 mm against phytopathogenic bacteria and fungi [16]. Endophytes have an antimicrobial activity that can produce metabolites, such as *celastramycins* [17], *kakadumycins* [18], and javanicin [19]. Reports from other previous research further revealed that endophytic bacteria and fungi have extracellular enzyme activity [20,21]. Endophytic bacteria and fungi synthesize extracellular enzymes as a resistance mechanism against disease, which helps to fend off pathogens and obtain food from their host plants. The extracellular enzymes that are commonly produced by endophytic bacteria and fungi are pectinase, amylase, cellulase, lipase, and protease. *Pseudomonas aeruginosa* was successfully isolated from the leaves of *Anredera cordifolia*, producing proteases, amylase, esterase, and cellulase [22]. *Bacillus subtilis P4* isolated from the *Pseudobrickellia brasiliensis* plant has protease and esterase activity [23]. Furthermore, the endophytic bacterium *Lysinibacillus xylanilyticus* has also been isolated from the *Chiliadenus Montanus* plant and potentially produces cellulase [24].*Vernonia anthelmintica, Saurauia scaberrinae,* and *Chromolaena odorata* are categorized as medicinal plants. The *Vernonia* genus, which belongs to the *Asteraceae* family with 1000 species, has been widely used for treating diabetes, parasitic worms, asthma, inflammation, wounds, skin diseases, malaria, cancer, and digestive disorders [25,26].

Various biological effects of *V. anthelmintica* plant extracts have also been reported, including anti-inflammatory, antimicrobial [27], antidiabetic and antihyperlipidemic activities [28]. Plants of *Saurauia* genus are widely distributed in Indonesia. One species that is considered quite widely known is *Saurauia bracteosa* which grows widely in the area of Lake Toba, North Sumatra, Indonesia [29]. Furthermore, Silalahi [30] reported that the leaves of *Saurauia vulcanii* were used for treating diarrhea, indigestion, and ethnomedicine for the Simalungun Batak sub-ethnic, in North Sumatra Province, Indonesia. Another species, *Saurauia laevigata*, is a *'honduran'* medicinal plant used to treat stomachache, in addition to *Saurauia scaberrinae*, which is found in Papua New Guinea, whose extracts *scaberrinae* contain alkaloid compounds [31]. Kirinyuh (*Chromolaena odorata*) plant is a wild plant easily found in our environment. The leaves of this plant contain several important compounds such as tannins, phenols, flavonoids, saponins, alkaloids, and steroids, while their essential oil contains α-pinene, cadinene, camphora, limonene, β-caryophyllene, and cadinol isomers [32]. Although the medicinal potential of these plants is well explored, unfortunately, research on endophytic bacteria and fungi from these plants has not been carried out optimally. Hence, the current review aims to explain the endophytic bacteria and fungi that have been studied from *Vernonia anthelmintica, Saurauia scaberrinae,* and *Chromolaena odorata* with the purpose of giving opportunities to the other researchers to conduct in-depth study on the plants that have not been studied yet. A better understanding of the relationship between endophytic microorganisms and their host medicinal plants will provide knowledge that can be exploited for the biotechnological production of better drugs from these plants.

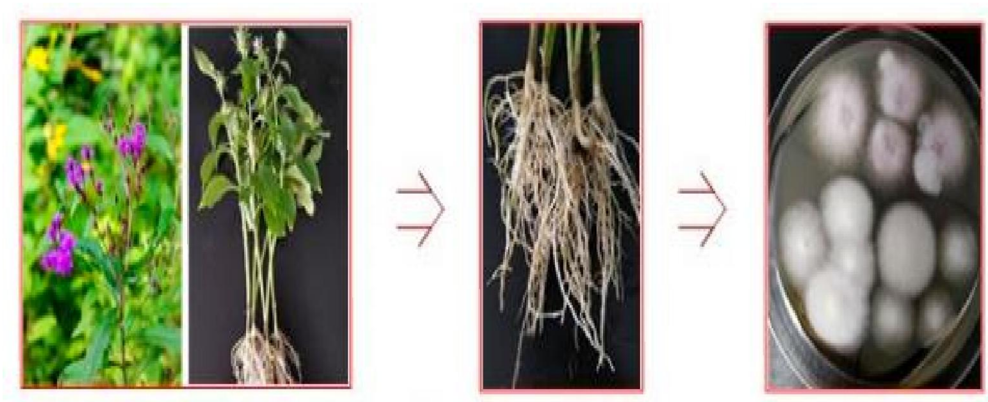
II. METHODS

The writing and preparation of this article were carried out based on a literature review obtained from online textbooks, research results, and scientific journals that have been published online. The research data used in this study are categorized as secondary data. Keywords used in online searches include endophytic bacteria, endophytic fungi, *Vernonia anthelmintic, Saurauia scaberrinae,* and *Chromolaena odorata*. Data that have been collected were further cohered to describe endophytic bacteria and fungi in medicinal plants of *Vernonia anthelmintica, Saurauia scaberrinae,* and *Chromolaena odorata*.

III. RESULT AND DISCUSSION

Vernonia anthelmintica plant is categorized as *Asteraceae* family and is widely distributed in subtropical and tropical areas throughout Asia and Africa [33]. This plant growth can reach 90 cm and grows widely throughout India, mostly in places near landfills to a height of 1500 m [34,35]. This plant has been generally used as a traditional medicine to cure quite many diseases including asthma, wounds, inflammation, skin diseases, kidney problems, eye itching, and hiccups [35,36].

This medicinal plant has also been reported to have various pharmacological activities such as antimicrobial, anticancer, antidiabetic, anti-inflammatory, analgesic, antipyretic, as well as diuretic and larvicidal activities [37]. This plant is commonly used in rural and urban areas of Bangladesh for treating diabetes [38]. Through phytochemical studies, it has been discovered that *V. anthelmintica* contains fatty acids, steroids, flavonoids, sesquiterpene lactones, carbohydrates, and terpenes [33,37].



Vernonia anthelmintica Roots of *Vernonia anthelmintica* Endophytic Bacteria

Fig 1. *Vernonia anthelmintica* plant. Rustamova et al. (2020)

Considering its benefits in the medical field, more research was conducted on *V. anthelmintica* plant by tracing its endophytic bacteria and fungi. In this case, *V. anthelmintica* was collected from the Xinjiang Autonomous Forest Region of the People's Republic of China in previous research [39]. Thus, Rustamova et al. [39] successfully isolated 25 bacterial stirpes from *V. anthelmintica* plant tissue, the isolates were identified as *M. endophyticus* VERA1, *B. megaterium* VERA2, *P. chlororaphis* VERA3, *P. kilonensis* VERA4, *S. pavanii* VERA5, *B. endophyticus* VERA6, *S. maltophlia* VERA7, *P. ananatis* VERA8, *B. atrophaeus* VERA5. *S. pavanii* VERA5 and *P. kilenensis* VERA4, showing antimicrobial activity against *E. coli*. The eight bacterial isolates except *S. pavanii* VERA5 and *B. atrophaeus* VERA9 showed moderate or strong inhibition against *S. aureus*. Previously, Emiliani et al. [40] observed the endophytic bacterium *Stenotrophomonas maltophilia* from the medicinal plant of *Lavandula angustifolia Mill*. Janardhan and Vijayan [41] also observed Pantoea ananatis from the medicinal plant of *Lantana camara* from Malaysia. Based on these studies, endophytic microorganisms associated with medicinal plants can synthesize biologically active compounds and show the same biological activity as their host cells (medicinal plant tissues) [42]. Furthermore, Akinsanya et al. [43] stated that endophytic bacteria associated with medicinal plants produce bioactive compounds with antimicrobial activity similar to their hosts.

Endophytes can also benefit their hosts by producing various natural products known as secondary metabolites. In this case, the endophytes can improve plant performance and protect it against insect pests and diseases infected from the soil or induce abiotic stress tolerance in plants [44,45]. Therefore, endophytes have a great potential to be used as a safe and cost-effective alternative to biopesticides and can be used as fertilizers that are considered constituents of sustainable agriculture. Furthermore, the medicinal plant *Saurauia scaberrinae* was also successfully collected from the area of Papua New Guinea. Hoffman et al. [46] successfully found a furandione compound named phomodione (4), which is produced by the endophytic fungus of *Phoma sp. Phomodione* (4) showed activity against *S. aureus* (MIC 1.6 µg/mL), *P. ultimum* (4–5 µg/mL), *S. sclerotiorum* (3–5 µg/mL), and *R. solani* (5– 8 µg/mL). As a reference, comparison was conducted between *phomodione* (4) activity and *cercosporamide* activity since their structure is similar. Cercosporamide is another natural product synthesized by *Phoma sp.* Cercosporamide, showing activity against *S. aureus* (MIC 2 g/mL). Not only that, *cercosporamide* can inhibit *Pythium ultimum* (3–4 µg/mL), plant pathogenic fungi from *oomycetes* class which are responsible for various diseases in many plants. *Cercosporamide* can also inhibit *Sclerotinia sclerotiorum* (5–8 µg/mL) which belongs to the plant pathogenic fungi of the *ascomycetes* class and *Rhizoctonia solani* (8–10 g/mL) of the plant pathogenic fungi of the *basidiomycetes* class.

Fig 2. Leaves of *Saurauia vulcani* plant. Pasaribu et al. [29]

The endophytic fungus *Phoma sp*. was also successfully isolated from the medicinal plant Artemisia princeps Pamp. Kim et al. [47] reported two new deriveatives of isochromanone compounds, (3S,4S)-3,8-dihydroxy-6-methoxy-3,4,5-trimethylisochroman-1-one and methyl (S)-18-hydroxy-6-methoxy-5-methyl-4a-(3-oxobutan-2-yl) benzoate isolated from endophytic fungus *Phoma sp. PF2* culture. Similarly, da Silva et al. [48] successfully isolated *Phoma sp*. URM 7221 endophytic fungi from the leaves of *Schinus terebinthifolius, Phoma sp.* URM 7221 has antimicrobial activity against human pathogenic bacteria, which are *S. aureus* and *Methicillin-Resistant Staphylococcus aureus* (MRSA). *Phoma sp.* is predominantly found in the stems of *Artemisia annua*, contributing 50% of the total fungi isolated from the stems of *Artemisia annua* which have cellulase activity. Based on the results of research conducted by Liu et al. [49] the cellulase activity of *Fusarium sp*. and *Phoma sp.* is significantly higher than *Humicola sp.* and *Alternaria sp*.

The endophytic bacteria of the medicinal plant *Chromolaena odorata* have also been previously studied. Mamangkey et al. [20] successfully reported 19 endophytic bacteria isolates from the roots, stems, and leaves of *Chromolaena odorata*. BECB3 isolates from stems and BECA8 were positive for their ability to produce β-amylase, α-amylase, cellulase, chitinase, and proteases. Most of the isolates produced proteases, except for isolates BECD3, BECD4, and BECA4. BECB3 produced significant hydrolytic enzyme activity, β-amylase (+++), α-amylase (++), cellulase (+++), chitinase (++) and protease (+++) compared to other isolates. In addition to bacteria, endophytic fungi were also successfully isolated from the leaves of *Chromolaena odorata*, which is CO-2AL3 isolate. The results of antimicrobial testing of the CO-2AL3 isolate extract showed antibacterial activity against *S. aureus, B. subtilis,* and *S. typhi* [50].

Fig 3. *Chromolaena odorata*

Gultom et al. [51] claimed that there were differences in the secondary metabolite compounds between young leaves and old leaves of kirinyuh *(Chromolaena odorata)* through gas chromatography. They found that there were more compounds obtained in old leaves of 22 bioactive compounds than the bioactive compounds found in young leaves, which are only 13 bioactive compounds. In this case, γ-sitosterol compounds are identified only in old leaves, while diisooctyl phthalate and Bis(2-ethylhexyl) phthalate, which belong to the saponin class are only found in young leaves. These bioactive compounds include flavonoids, terpenoids, saponins, phenols, alkaloids, and steroids [51].

IV. CONCLUSION

Endophytic bacteria and fungi co-evolved with plants and stablished a special relationship with their host, living inside the healthy tissues and being an important component of plant micro-ecosystems. In this review, we summarized recent studies on the diversity of endophytic bacteria and fungi derived from traditional medicinal plants. Briefly, endophytic bacteria from *V. anthelmintica* were identified as *M. endophyticus* VERA1, *B. megaterium* VERA2, *P. chlororaphis* VERA3, *P. kilonensis* VERA4, *S. pavanii* VERA5, *B. endophyticus* VERA6, *S. maltophlia* VERA7, *P. ananatis* VERA8, *B. atrophaeus* VERA5. *S. pavanii* VERA5 and *P. kilonensis* VERA4, which have antimicrobial activity against *E. coli*. Among these eight bacterial isolates, except *S. pavanii* VERA5 and *B. atrophaeus* VERA9, showed moderate or strong inhibition against *S. aureus*. Furthermore, endophytic fungi *Phoma sp.*

Was successfully isolated from the *Saurauia scaberrinae* plant, which produced *phomodione* (4) and showed activity against *S. aureus, P. ultimum, S. sclerotiorum* and *R. solani*. Cercosporamide is another natural product synthesized by *Phoma sp. Cercosporamide* which further showed activity against *S. aureus*. In this case, there were 19 isolates of endophytic bacteria derived from the roots, stems, and leaves of *Chromolaena odorata*. BECB3 isolates from stems and BECA8 were positive for their ability to produce β-amylase, α-amylase, cellulase, chitinase, and proteases. Endophytic fungi were also isolated from the leaves of Chromolaena odorata, which is CO-2AL3 isolate. In this case, antimicrobial activity was shown by the CO-2AL3 isolate extract against *S. aureus*, *B. subtilis*, and *S. typhi*. This report confirms that the bioactive compounds in medicinal plants are a habitat for specific endophytic bacteria and fungi that survive to live in medicinal plant tissues. However, not all types of endophytic bacteria and fungi can live in these tissues, resulting in secondary metabolites produced by endophytic bacteria and fungi that are similar to the plants they live in.

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