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Review Article

Bioactivity and Metabolites Compounds of Medicinal Plants Endophytic Fungi in Indonesia

Eka Sukmawaty[1,6], Abdul Karim[2], Zaraswati Dwyana[5], Hasnah Natsir[2], Harningsih Karim[7], Ahyar Ahmad[2,3,4]*, Siti Halimah Larekeng[4,8]
1)Doctoral Program, Department of Chemistry, Faculty of Mathematics and Natural Science, Hasanuddin University, 90245, Makassar, Indonesia
2)Department of Chemistry, Faculty of Mathematics and Natural Science, Hasanuddin University, 90245, Makassar, Indonesia
3)Research and Development Centre for Biopolymers and Bioproducts; LPPM, Hasanuddin University, Makassar, 90245, Indonesia
4)Research Collaboration Center for KARST Microbes BRIN-LPPM, Hasanuddin University, Makassar, 90245, Indonesia
5)Department of Biology, Faculty of Mathematics and Natural Science, Hasanuddin University, 90245, Makassar, Indonesia
6)Department of Biology, Faculty of Science and Technology, UIN Alauddin Makassar, 92118, Makassar, Indonesia
7)Department of Pharmacy, School of Pharmacy YAMASI, Makassar, Indonesia
8)Faculty of Forestry, Hasanuddin University, Makassar, 90245, Indonesia
* Corresponding author, email: ahyarahmad@gmail.com

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ABSTRACT
Indonesia is rich in diversity of medicinal plants, vital in traditional medicine and the pharmaceutical industry. However, overharvesting, along with population growth, land use changes, deforestation, and climate change, endanger these plants. This review investigates the potential of endophytic endosymbiont as an alternative. These endosymbionts can synthesise bioactive compounds similar to those found in medicinal plants. This study compiled data from various sources on endophytic fungi and their bioactivity. The review aims to categorise Indonesian medicinal plants, to identify their associated endophytic fungi from different plant parts, and to assess their bioactivity. The results revealed numerous medicinal plant families and a variety of endophytic fungi isolated from fruits, leaves, twigs, bark, roots, and rhizomes. These fungi exhibited bioactivities, including antioxidant, anticancer, antidiabetic, and antimicrobial effects, with metabolites such as alkaloids, flavonoids, peptides, phenols, polyketides, quinones, steroids, and terpenoids. *Fusarium* and *Colletotrichum* were the most common endophytic fungi found. Notably, the biological activity was consistent among endophytic fungi from various host organs, but variations were observed according to the host's geographical origin. This suggests that Indonesia's diverse geography influences metabolite production and activity. However, the same host plant may harbour different species in distinct organs. These findings indicate that endophytic fungi within medicinal plants represent a promising source of bioactive compounds for future Indonesian medicine production. Future research should explore metabolite compounds and bioactivity across different geographical regions.

INTRODUCTION
As the demand for herbal medicines, natural health products, and the production of secondary metabolites expands, the usage of medicinal plants is growing quickly throughout the world (Chen et al. 2016). In

developing nations, medicinal plants and their derivatives continue to be the primary sources for treating a variety of diseases due to their affordability and accessibility (Verma & Singh 2008). The distribution of medicinal plants worldwide encompasses over 50,000 plant species that find application in cosmetic and medicinal products, constituting more than a tenth of all plant species (Kopaei 2012). Even though conventional medication is readily available in many Asian nations, traditional medicine is still commonly used. Traditional medicine, also known as indigenous medicine or folk medicine, is a community-based technique of treatment that predates the invention of modern medicine (Gunjan et al. 2012). Extraction and cultivation of medicinal plants are essential activities in many Asian nations, such as Bangladesh, China, India, Nepal, Pakistan, Myanmar, and Indonesia (Astutik el al. 2019). An estimated half a million plant species in India have been examined phytochemically for their biological or medicinal properties (Bamola et al. 2018). China has employed 8000 types of medicinal herbs since the Paleolithic Age (Huang 2011). Approximately 472 species plants have been used as medicinal plants in Myanmar (DeFilipps & Krupnick 2018). Over 2187 plant species in Thailand have been identified as having therapeutic value (Phumthum et al. 2019). As a megadiverse nation, Indonesia possesses between 2500 and 7500 kinds of medicinal plants that are widely used as medications and cosmetics throughout the country (Cahyaningsih et al. 2021a).

In Indonesia, where a large quantity of medicinal herbs thrives, a significant portion of the population, particularly those residing in rural areas, traditionally depend on "jamu" or herbal medicines for disease treatment. This practice has led to the development of jamu production on an industrial scale (Elfahmi et al. 2014). However, this increased demand has the potential to cause overharvesting for the medicinal trade, resulting in the depletion of medicinal plant resources. Coupled with human population growth, land conversion, deforestation, and the impacts of climate change, the conservation of Indonesian plant species becomes both challenging and costly (Cahyaningsih et al. 2021b). Endophytic endosymbiont microorganisms present an alternative strategy. They possess the capability to synthesise bioactive compounds similar that produced by their host plants (Alnweiri 2021). Endophytes, which include microorganisms like fungi and bacteria, establish a unique symbiotic relationship with their host plants, residing within the internal plant parts (Pimentel et al. 2011). These microorganisms remain inconspicuous, causing no visible signs of infection or disease (Zheng et al. 2021). Consequently, they represent a hidden microbial world within plants, often overlooked compared to their more pathogenic counterparts. Yet, they constitute an underutilised resource for the discovery of novel therapeutic compounds (Kharwar et al. 2011). Endophytes are a valuable source of natural compounds due to their remarkable ability to produce a diverse range of biologically active substances. Compared to other endosymbiotic microorganisms, they generate a wide array of secondary metabolites. These compounds are the subject of ongoing research for various medicinal and industrial applications (Sudha et al. 2016). Endophytes are known to synthesise various classes of metabolites, including alkaloids, cytochalasines, furandiones, glycosides, isocoumarins, isoprenoids, lipids, perylene derivatives, phenols, polyketides, peptides, proteins, steroids, terpenoids, shikimates, and xanthones (Kharwar et al. 2011; Joseph & Priya 2011; Jalgaonwala et al. 2017; Rajamanikyam et al. 2017).

Endophytic fungus produces similar bioactive compounds from their host plants and therefore it is hypothesised that the complexities of fungal endophytes and host plant relationships vary across microorganisms and hosts (Verma et al. 2009). Ludwig-Müller (2015) delineates the multifaceted interactions between plant and endophytes at various levels: (a) endophytes stimulate host metabolism, (b) the host reciprocates by stimulating endophyte metabolism, (c) the host and endophyte collaborate in distinct metabolic pathways, (d) both the host and endophyte may engage in the metabolism of endophyte products, and (e) secondary chemicals from the host can be metabolised by the endophyte. These options can apply to one or many enzymatic stages in the biochemical transformation process.

Numerous host plants have been explored for their endophytic fungi, with most of them found to harbour diverse fungal endophyte populations. The richness and diversity of these fungal endophytes are intricately linked to environmental factors such as rainfall and air humidity where the host plants thrive (Gigantea et al. 2011).

Endophytic fungi have proven to be prolific sources of novel bioactive compounds, demonstrating antibacterial, cytotoxic, anticancer, and insecticidal properties (Zheng et al. 2021). As highlighted by Newman & Cragg (2020) over 70% of anticancer and antibacterial medications derived from endophytic fungus contain natural bioactive compounds or their derivatives. Additionally, a wide range of endophytes hold potential for producing compounds that enhance plant growth and stimulate plant hormones. They are capable of generating chemicals with applications in agriculture, such as nematocidal and insecticidal properties, iron-chelating agents, and resilience to abiotic stress (Sharma et al. 2021).

Based on that information, it is necessary to determine the pharmacological potential of endophytic fungi isolated from Indonesian medicinal plants as natural bioactive source. This comprehensive review aims to elucidate the utilisation of endophytic fungi as primary resources for the pharmaceutical industry. According to Suhel (2022), Indonesia is still importing raw materials for medicines to meet the increasing demand for the medicines industry. Utilising endophyte fungi from Indonesian medicinal plants is a solution to the availability of raw materials obtained domestically, preventing the extinction of plants which are Indonesia's rich biodiversity and preventing ecological damage due to exploration of perennial plants which take a long time to grow. This paper review provides a thorough exploration the bioactive metabolite from Indonesia medicinal plants diversity from across the Indonesia archipelago.

INDONESIA MEDICINAL PLANTS

Indonesia has a great diversity in natural resources, including abundance of medicinal plants. It is the second largest tropical country after Brazil with a total of 40 thousand plants species are found Indonesia (Zakariya et al. 2020). The application of medicinal plants is a knowledge passed down from generation to generation, and still maintained as local wisdom in many tribes in Java, Sumatra, Kalimantan, Sulawesi, and Papua Island. Batak karo tribe in North Sumatera uses *Hibiscus rosa-sinensis* (kembang sepatu), *Ceiba pentandra* (kapuk), *Etlingera elatior* (kecombrang) as medicine to cure fever (Silalahi & Nisyawati 2018). Sundanese tribe in Java still use herbs as medicinal treats such as *Ageratum conyzoides* (babandotan), *Pluchea indica* (baluntas), *Indian jujube* (daun binara), *Lagerstroemis speciosa* (bungur), *Physalis Angulata* (cecendet), *Syzygium aromaticum* (cengkeh), *Phyllanthus acidus* (cereme), *Cogon grass* (eurih), *Graptophyllum pictum* (handeuleum,), *Bidens pilosa* (hareuga), and *Plumbago zeylanica* (ki encok) (Suganda et al. 2018). Keladi (*Colocasia esculenta* L) appears to be the most useful plant as medicine in Dayak Tribe, West Kalimantan (Supiandi et al. 2019), whereas Dayak Tribes in North Kalimantan used plants from *Asteraceae* family as the highest proportion medicinal herb for treating pain (Novrianti et al. 2020). In South Sulawesi, *Allium cepa* is the most used plant at Rongkong community in North Luwu District (Mustofa et al. 2020). Papua has a diverse biodiversity, and there are various native plants which utilised as traditional medicine by Papua people, such as *Myrmecodia pendans* Merr, *Asteromyrtus symphyocarpa* Linn. Craven (Winara et al. 2015), and *Allophylus cobbe* (L.) Raeusch (Ibo & Arifa 2021).These plants are solely utilised as traditional medicine by the Papuan tribe. Since malaria is an endemic disease in Papua, they use *Andrographis paniculata* (Burm. f.) Nees, *Carica papaya* L., *Alstonia scholaris* (L.) R. Br., and *Physalis minima* L. as antimalaria traditionally Other common medicinal plants in Indonesia community listed in Table 1.

ENDOPHYTIC FUNGI AND THEIR BIOACTIVE POTENTIAL

Endophytic Fungi Ecological and Diversity from Indonesia Medicinal Plants

Endophytic fungi, unlike mycorrhizal fungi that mainly inhabit the root systems of plants, reside within various plant tissues, including roots, stems, and leaves. They establish a symbiotic relationship with their host plants. Unlike mycorrhizal fungi, which mainly reside in the root systems of plants, endophytic fungi colonize the entire plant, both intercellularly and intracellularly (Rodriguez et al. 2009; Schulz & Boyle 2014). The structural changes in endophytic root fungus colonization indicate varying degrees of colonization. This colonization pattern is often observed in intercellular sections, the outer cortical regions, and the epidermis of plant roots. Endophytes have been detected both adhering to the root

Table 1. Common Medicinal Plants in Indonesia.

No	Local Name	Scientific Name	Location	Family	References
1	Mahoni	*Swietenia mahagoni* (L.) Jacq.	North Sumatra and Papua Island	Meliaceae	Situmorang et al. 2015; Rahmawaty et al. 2019; Budiarti et al. 2020
2	Kemiri	*Aleurites moluccana* (L.) Willd.	South Aceh	Euphorbiaceae	Suwardi et al. 2020
3	Kelapa	*Cocos nucifera* L.	Southeast Sulawesi, West Kalimantan, and East Java	Arecaceae	Supiandi et al. 2019; Jadid et al. 2020; Fachruddin et al. 2021
4	Jeruk nipis	*Citrus aurantifolia* (Christm.) Swingle, orth.	East Java	Rutaceae	Shalas et al. 2021
5	Jambu Biji	*Psidium guajava* L.	South Sumatra	Myrtaceae	Kurniati et al. 2019
6	Jamblang	*Syzygium cumini* L.	Aceh		Gemsih et al. 2017
7	Jahe	*Zingiber officinale* Rosc.	Indonesia	Zingiberaceae	Ginting et al. 2013; Harwoko et al. 2021
8	Lengkuas	*Alpinia galanga* L.	Bali		Raniningsih & Sandy 2018
9	Pegagan	*Centella asiatica* (L.) Urban.	Bengkulu	Apiaceae	Radiastuti et al. 2019
10	Kelor	*Moringa oleifera* Lam.	South Sulawesi	Moringaceae	Rohadi et al. 2019
11	Alang-alang	*Imperata cylindrica* (L.) Beauv.	Indonesia	Poaceae	Jamilatun & Shufiyani 2019
12	Dewadaru	*Mesua ferrea* L.	Banyumas, Indonesia	Callophylaceae	Hartanti 2015
13	Merica	*Piper nigrum* Linn	Kutai Kartanegara, East Kalimantan	Piperaceae	Sopialena et al. 2018
14	Srikaya	*Annona squamosa* L.	Indonesia	Annonaceae	Yunianto et al. 2012
15	Kayu secang	*Caesalpinia sappan* L.	South Sulawesi	Caesalpiniaceae	Hafsan et al. 2018

epidermis and within the cell walls (Pal et al. 2020). Plant-fungal partnerships are highly symbiotic, a result of the close adaptation of host plants and their fungal companions, developed through coevolution and cohabitation, strengthening their genetic compatibility (Mengistu 2020). Successful endophyte colonisation depends on the compatibility of interactions between plant and microbe. Upon an endophyte's invasion, the host plant recognises it and initiates a signaling molecule exchange (Khare et al. 2018). Fungal endophytes, with a diverse range of host interactions, may employ various strategies to penetrate the host's internal systems. These strategies include altering plant elicitors, producing toxic metabolites, and suppressing the host's immune response (Selim et al. 2012).

Endophytic fungi must overcome the plant's initial defense mechanisms to establish a successful infection. They achieve this by manipulating host cells to form structures that enable them to penetrate plant tissues while preserving host cell integrity for a long-lasting association (Kogel et al. 2006). The first stage of plant-microbe interaction, which includes endophytes, involves the detection of plant exudates in the soil. There is a theory that plants can interact with microorganisms by releasing exudates, which are a mixture of substances such as carbohydrates, organic acids, and amino acids. The composition of exudates can vary depending on the plant species and its environmental conditions, whether they are biotic or abiotic (Haldar & Sengupta 2015). Mehmood et al. (2018) discovered that the IAA hormone and flavonoids are crucial participants in the intricate chemical conversation between plant roots and endophytic fungus. The use of IAA as an aerial spray to corn seedlings enhanced the roots' ability to interact with fungi and their effective colonisation of the roots. IAA application increased the concentration of flavonoids in endophyte-infected root exudates.

Fungal endophytes have been isolated from a wide range of plant biological environments, from dry, arid regions to arctic areas, and from temperate forests to tropical woodlands, savannahs, grasslands, and croplands. They have been discovered in a diverse range of plants, ranging from Angiospermae to Gymnospermae, mosses to ferns, and from simple to complex plants (Rashmi et al. 2019). Temperature, humidity, and soil nutrition levels are the key variables in determining secondary metabolite types and amounts produced by the plants, which in turn affected the population structure of the fungal endophytic (Jia et al. 2016). Endophytic assemblages vary in composition depending on region and host species. Endophytic communities have been discovered in various host lineages (Weig et al. 2013). This might be due to the actions of antifungal metabolites such flavonoids (Unterseher et al. 2016) and suitable populations of host and fungus are necessary for a successful infection (Guerreiro et al. 2022). Plant species adjust their biological systems under competitive and unfavourable ecological situations by creating diverse defense responses, which are mostly evident in the creation of protective secondary metabolites. These metabolites also help to create host defensive mechanisms, which improves the host's ability to adapt to a wide range of biogeographical habitats (Alam et al. 2021). Several endophytic fungi in different ecosystem are presented in Table 2.

Isolation of bioactive compounds directly from medicinal plants requires a lot of biomass which has an impact on the destruction of biological resources due to limited raw materials for herbal medicines (Godlewska et al. 2021). Therefore, one way of using biotechnology approach to increase the production of secondary metabolites from medicinal plants is by using endophytic microbes, namely endophytic fungi. Ogbe et al. (2020) elucidated the capacity of endophytic fungi to synthesise

Table 2. Endophytic fungi isolated from various plant in different ecosystem.

Most dominant Fungal endophytes	**Host plants**	**Environmental condition**	**References**
Alternaria sp., *Asperigillus* sp., and *Penicillium* sp.	Desert medicinal plants (*Artemesia sieberii* L., *Citrillus colocynthis* (L.) Schrad., and *Moringa peregrina* (Forssk.) Fiori)	Arid environment	Rehman et al. 2019
Neocamarosporium, *Preussia*, *Alternaria*, *Ascochyta*, *Phoma*, *Comoclathris*, *Neomicrosphaeropsis*, *Aureobasidium*, *Pleospora*, and *Fusarium*	Arid plant of Andalusia (*Limonium majus* (Boiss.) Erben or *Moricandia foetida* Bourg. ex Coss., *Helianthemum almeriense* Pau, *Centaurea dracunculifolia* Dufour., and *Euzomodendron bourgeanum* Cosson.)	Arid environment	González-Menéndez et al. 2018
Aspergillus sp., Botryosphaeria sp., Preussia sp., Phoma sp., Aureobasidium sp., Penicilliumc sp., and Chaetomium sp.	*Simmondsia chinensis (Link) C.K. Schneid., Phoradendron californicum Nutt., Parkinsonia microphylla Torr.,* and *Larrea tridentata (de Candolle) Coville.*	Arid environment	Massimo et al. 2015
Aeopora sp., *Sebacina* sp., *Knufi* sp., *Tomentella* sp., and *Penicillium* sp.	*Argania spinosa* (Linnaeus) Skeels. root	Arid environment	Noui et al. 2019
Pezizomycotina sp., *Monosporascus ibericus*, and *Alternaria eichhorniae*	*Kalidium foliatum* (Pall.), *Salsola nitraria* Pall., *Seriphidium santolinum (Schrenk) Poljakov, Reaumuria songarica (Pall.) Maxim., Ceratocarpus arenarius* L., *Suaeda acuminata (C.A.Mey.) Moq., Suaeda salsa* (L.) Pall., *Eragrostis minor* Host, *Peganum harmala* (L.), and *Bassia dasyphylla (Fisch. & C.A.Mey.) Kuntze.*	Arid environment	Li et al. 2020
Cladosporium cladosporioides, Fusarium oxysporum, Acremonium implicatum, Aureobasidium pullulans, Trichoderma viride, Chrysonilia sitophila, and *Aspergillus flavus*	Cactus *Cereus jamacaru* DC.	Tropical forest	Bezerra et al. 2013
Acrocalymma sp., *Fusarium* sp., *Tolypocladium* sp., *Penicillium* sp, *Talaromyces* sp., *Exophiala* sp., *Dictyosporium* sp., *Pseudochaetosphaeronema* sp., *Mariannaea* sp., *Trichoderma* sp., *Mycoleptodiscus* sp., *Acrocalymma* sp., *Tolypocladium* sp., *Penicillium* sp., *Exophiala* sp., *Pseudochaetosphaeronema* sp., *Mariannaea* sp., and *Mycoleptodiscus* spp.	*Paraserianthes falcataria* (L.) Nielsen.	Tropical forest	Maulana et al. 2018
Talaromyces, Phyllosticta, Diaporthe, and *Colletotrichum.*	*Myracrodruon urundeuva Fr. Allem.*	Tropical dry forest	de Pádua et al. 2019

Table 2. Contd.

Most dominant Fungal endophytes	Host plants	Environmental condition	References
Aspergillus flavus, *Altenaria* sp., *Bionectria ochroleuca*, *Colletotrichum acutatum*, *Cladosporium* sp., *Cochliobolus sativus*, *Diaporthe amygdali Fusarium Oxysporum*, *Guignardia mangiferae*, *Phomopsis* sp., *Phyllosticta gardeniicola*, *Trichoderma harzianum*, *Tricharina gilva*, and *Nigrospora oryzae*.	*Warburgia ugandensis* Sprague	Tropical forest	Mbilu et al. 2018
Chrysosporium sp., *Curvularia lunata*, *Penicillium* sp., *Geotrichum candidum*, and *Trichoderma* sp.	*Caesalpinia sappan* L.	Tropical forest	Hafsan et al. 2018
Alternaria sp, *Pestalotiopsis* sp., *Fusarium* sp., *Nigrospora* sp., *Phoma* sp., and *Xylaria* sp.	*Rhizophora mucronate* Lam.	Mangrove forest	Hamzah et al. 2018
Auriculibuller, *Yamadazyma*, *Pseudoplectania*, and *Simplicillium*	Mangrove trees	Mangrove ecosystem	Yao et al. 2019
Genera *Pestalotiopsis* and *Phomopsis*	Rhizophoraceae mangrove plant	Mangrove ecosystem	Xing & Guo 2011
Aspergillus sp., *Phoma* sp., and *Penicillium* sp.	*Avicennia marina* (Forssk.) Vierh.	Mangrove ecosystem	Selvakumar et al. 2014
Guignardia sp. and *Colletotrichum gloeosporioides*	*Rhizophora mangle* L., *Avicennia schaueriana* Stapf & Leechm. ex Moldenke., and *Laguncularia racemose* (L.) C.F. Gaertn.	Mangrove ecosystem	Costa et al. 2012
Aspergillus niger, *Acremonium* sp., *Chaetomium* sp., *Cladosporium* sp., *Fusarium* sp., Phomopsis sp., and *Xylaria* sp.	Seaweeds	Marine ecosystem	Ahamed & Murugan 2019
Trichoderma sp.	*Padina* sp.	Marine ecosystem	Handayani et al. 2019
Aspergillus sp., *Fusarium* sp. and *Penicillium* sp,	*Hypnea musciformis (Wulfen) J.V.Lamouroux*, *Sargassum crassifolium* J. Agardh., *Dictyota dichotoma (Hudson) J.V.Lamouroux*, and *Caulerpa peltata J.V.Lamouroux*.	Marine Ecosystem	Officer & Road 2020

metabolites influenced by their host plants, rendering them a promising and dependable source of secondary metabolites. The isolation of endophytic fungi from diverse plant organs serves the purpose of identifying bioactive agents that produce secondary metabolites, often found in specific plant organs, with crucial medicinal potential. Plants produce secondary metabolite compositions in various parts, such as fruits, leaves, stems, and roots (Astuti & Respatie 2022). Endophytic fungi have been discovered from a diverse range of medicinal plants. These endophytic fungus generated a diverse spectrum of industrially significant bioactive compounds (Rana et al. 2020). Indonesia has abundant medicinal plants that used as traditional medicine for a long time. The exploration of their endophytic fungi also become the focus of several researchers. Fungi, genus of *Fusarium* and *Colletotrichum* appears as the most dominant endophytes found in Indonesia medicinal plants. However, endophytic fungi do not show host specifications for certain plant hosts or certain organs. Diverse endophytic fungi that have successfully isolated from Indonesia medicinal fungi are listed in Table 3.

Table 3. Endophytic Fungi Isolated from Indonesian Medicinal Plants.

Plant Species	**Organ**	**Endophytic Fungi**	**References**
Calopogonium mucunoides Desv.	Leaves and stems	*Phomopsis* sp., *Corynespora* sp., *Rhizoctonia* sp., *Helicosporium* sp., *Curvularia* sp., *Acremonium* sp., *Torulomyces* sp., *Gliocladium* sp., *Humicola* sp., *Gloeosporium* sp, *Phoma* sp, *Tripospermum* sp., *Aureobasidium* sp., *Colletotrichum* sp., *Fusarium* sp., and *Sclerotium* sp.	Fitriarni & Kasiamdari 2018
Zingiber officinale Rosc.	Leaves, rhizome, roots, and stem	*Acremonium macroclavatum*, *Lecanicillium kalimantanense*, *Myrothecium verrucaria*, *Trichoderma harzianum*, *Beltraniella* sp., *Cochliobolus geniculatus*, *Colletotrichum gloeosporoides*, *Neonectria punicea*, *Periconia macrospinosa*, *Rhizopycnis vagum*, *Glomerella cingulate*, and *Talaromyces assiutensis*	Ginting et al. 2013; Harwoko et al. 2021
Centella asiatica (L.) Urban.	Stolons, leaves, roots, and petioles	*Acrocalymma vagum*, *Aspergillus oryzae*, *Aspergillus austroafricanus*, *Peroneutypa scoparia*, *Chaetomium globosum*, *Ceratobasidium* sp., *Phoma multirostrata*, *Fusarium* sp., *Colletotrichum karstii*, *C. gigasporium*, *C. tabaci*, *Colletotrichum siamense*, *Eutypella* sp., *F. oxysporum*, *F. falciforme*, *Penicillium capsulatum*, *F. keratoplasticum*, *F. striatum*, *Ceratobasidium cornigerum*, *Earliella scabrosa*, *Perenniporia tephropora*, *Perenniporia* sp., *Phanerochaete chrysosporium*, *Phanerochaete stereoides*, *Phyllosticta capitalensis*, *Phomopsis asparagi*, *Mycochaetophora gentinae*, *Phialemoniopsis* sp., *Talaromyces* sp., and *Trichaptum* sp.	Radiastuti et al. 2019
Moringa oleifera Lam.	Lamina, petiole, and stem	*Cladosporium* sp., *Colletotrichum* sp., *Fusarium* sp., *Phomopsis* sp., and *Phyllosticta* sp.	Rohadi et al. 2019
Syzygium cumini L.	Leaves	*Colleotrichum* sp., *Acremonium* sp., *Fusarium* sp., *Macrophopmina* sp., *Dactylella* sp., *Paecilomyces* sp., and *Nigrospora* sp.	Gemsih et al. 2017
Imperata cylindrica (L.) Beauv	Flowers, stem, and leaves	*Fusarium* sp. and *Mucor* sp.	Jamilatun & Shufiyani 2019
Alpinia galanga L	Rhizome	*Trichoderma viridae*, *Trichoderma harzianum*, and *Fusarium oxyforum*	Raniningsih & Sandy 2018
Mesua ferrea L.	Leaves and twigs	*Penicillium* sp. and *Aspergillus* sp.	Hartanti 2015
Piper nigrum Linn	Leaves and roots	*Aspergillus* sp., *Fusarium* sp., *Nigrospora* sp., and *Trichoderma* sp.	Sopialena et al. 2018
Guazuma ulmifolia Lam.	Leaves	*Curvularia affinis*, *Lasiodiplodia mahajangana*, *Talaromyces trachyspermus*, *Diaporthe tectonae*, and *Parengyodontium album.*	Sukarno et al. 2021
Hydrocotyle verticillata Thunb.	Leaves	*Muyocopron laterale* and *Didymella coffeae-arabicae*	Sukarno et al. 2021
Cinchona calisaya Wedd.	Flowers, leaves, petioles, stems, bark, and roots	*Fusarium oxysporum. Diaporthe* sp., *Neofussicoccum* sp., *Guignardia mangiferae*, *Colletotrichum gloeosporioides*, and *C. Brasiliense.*	Hidayat et al. 2019

Table 3. Contd.

Plant Species	**Organ**	**Endophytic Fungi**	**References**
Annona squamosa L.	Seeds	*Fusarium* sp. and *Nectria rigidiuscula*	Yunianto et al. 2012
Curcuma longa L.	All plant organs	*Phaeosphaeria ammophilae*, *Phanerochaete chrysosporium*, *Fusarium verticillioides*, *Fusarium solani*, *Fusarium proliferatum*, *Fusarium oxysporum*, *Arthrobotrys foliicola*, *Daldinia eschscholzii*, and *Cochliobolus kusanoi.*	Septiana et al. 2017
Morinda citrifolia Linn.	Fruits and leaves	*Stemphylium solani*, *Leptosphaerulina australis*, and *Xylaria* sp.	Wu et al. 2015
Caesalpinia sappan L.	Stem	*Geotrichum candidum*, *Trichoderma* sp., *Penicillium* sp., *Chrysosporium* sp., and *Curvularia lunata.*	Hafsan et al. 2018

Indonesia Medicinal Plant Endophytic Fungi Produced Antioxidant

Antioxidants are chemicals that, in very low quantities, dramatically block the role of oxidation in the targets (Rasheed & Azeez 2019). The antioxidant properties of certain polyphenolic compounds, like flavonoids, are often linked to the presence of aromatic phenolic rings. These rings have the ability to donate electrons and to transfer hydrogen atoms to free radicals, acting as scavengers of free radicals, inhibitors of the formation of single oxygen, and reducing agents (Wu et al. 2018).

Endophytic fungi are known to produce a variety of antioxidant chemicals, that are responsible for host plant stress tolerance (Manganyi & Ateba 2020). Many studies have been conducted to investigate the different fungal species found in medicinal plants, and the results have been promising (Toghueo & Boyom 2019). This section discusses the antioxidant effects of crude extracts and compounds obtained from endophytic fungi associated with several Indonesia medicinal plants.

Antioxidants activity have been observed from endophytic fungi that isolated from turmeric. Turmeric has been used as traditional medicine in Indonesia to treat many diseases include related to free radical diseases (Subositi & Wahyono 2019; Permatananda et al. 2021; Rahmat et al. 2021). Septiana et al. (2020) have been discovered that the ethyl acetate extracts of endophytic fungi from turmeric flowers have antioxidant activity. Moreover, the extracts of single and mixed cultures demonstrated antioxidant activity, with IC_{50} values ranging from 247.90 to 634.64 g/mL. Endophytic fungi isolated from various tissues of turmeric have also been shown to have antioxidant properties. Endophytic fungi extracts from turmeric rhizome, root, leaves, and also turmeric stem, exhibited antioxidant activity in ethyl acetate (Widowati et al. 2016; Eris & Simanjuntak 2017; Septiana et al. 2019; Septiana et al. 2020). *Chrisonilia sitophila*, *Acremonium* sp., and *Penicillium* sp. were isolated from Kandis Gajah twigs, a traditional medicine in south Sumatera, as endophytic fungi. The antioxidant bioactive molecule generated by *Acremonium* sp was sesquiterpene 3,5-dihydroxy-2,5-dimethyltrideca-2,9,11-triene-4,8-dione, according to NMR studies (Elfita et al. 2012). Other endophytic fungi that produced antioxidant are listed in Table 4.

Endophytic Fungi Produced Anticancer

Endophytic fungi have emerged as a consistent and abundant source of potential anticancer agents, marking a significant contribution for anticancer drug development (Uzma et al. 2018). These fungi are at the forefront of the search for novel bioactive secondary metabolites with cytotoxic properties, significantly contributing to the quest for new plant-derived anticancer medications. Research has identified approximately 19

Table 4. Antioxidant Compounds Produced by Endophytic Fungi from Medicinal Plants in Indonesia.

Endophytic Fungi	Host	Compound	References
Cladosporium tenuissimum	*Swietenia mahagoni* (L.) Jacq.	5-hydroxy-2-oxo-2H-Piran-4-yl methyl acetate	Fadhillah et al. 2019
Lasiodiplodia venezuelensis	*Syzygium samarangense* L.	5,7-dihydroxy-6,8-dimethyl flavanone	Budiono et al. 2019
Fusarium sp. and *Colletotrichum* sp.	*Physalis angulata* L.	Not identified yet	Palupi et al. 2021
Apodus oryzae and *Diaporthe* sp.	*Aquilaria malaccensis* Lam.	Not identified yet	Hidayat et al. 2019
Aspergillus minisclerotigens and *Aspergillus oryzae*	*Mangifera casturi* Kosterm.	Dihydropyran and 4H-Pyran-4-one,5-hydroxy -2-(hydroxymethyl-(CAS) Kojic acid	Nuraini et al. 2019
Trichordema reecei	*Syzygium aqueum* (Burm.f.) Alston.	(4-hydroxy-3-(4-hydroxyphenyl)-5 oxo-tetrahydrofuran-2-yl) methyl acetate	Habisukan et al. 2021
Geotrichum candidum, *Trichoderma* sp., *Chrysosporium* sp., *Curvularia lunata* and, *Penicillium* sp.	*Caesalpinia sappan* L.	Not identified yet	Hafsan et al. 2018
Neofusicoccum parvum	*Cinnamomum burmanni (Nees &Th. Nees).*	Not identified yet	Rachman et al. 2018
Fusarium oxysporum	*Dahlia variabilis* Willd.	Not identified yet	Marlinda et al. 2019
Phyllosticta sp., *Colletotrichum* sp., *Phomopsis* sp., *Phoma* sp., and *Lasiodiplodia* sp.	*Vernonia amygdalina* Del.	Not identified yet	Hidayat et al. 2019
Acremonium sp.	*Garcinia griffithii* T. Anderson	3,5-dihydroxy-2,5-dimethyltrideca-2,9,11-triene-4,8-dione	Elfita et al. 2012

chemical families of fungal secondary metabolites known to exhibit anticancer effects against 45 different cell lines (Bano et al. 2016). Among these bioactive compounds, figures such as paclitaxel, podophyllotoxin, camptothecin, ergoflavin, swainsonine, sclerotiorin, flavone chrysin, torreyic acid, vincristine, and vinblastine have been isolated from endophytic fungi, offering promising prospects in anticancer drug development (Ejaz et al. 2020) (Figure 1).

In Indonesia, endophytic fungi within medicinal plants have shown great promise as sources of anticancer compounds. Notably, endophytic fungi from soursop leaves, isolated in West Java, demonstrated anticancer potential against the MCF-7 cell line with an IC_{50} of 19.20 (Minarni et al. 2017). *Hypomontagnella monticulosa* Zg15SU, originating from *Zingiber griffithii* Baker in North Sumatera, exhibited cytotoxicity against cancer cell lines HCT116, NBT-T2, and Panc-1, as determined through in vitro MTT proliferation experiments (Lutfia et al. 2021). Furthermore, endophytic fungi *Eutypa linearis* from *Coleus amboinicus* (Lour.) were found to produce compounds such as benzenemethanol, 4-nitro-(p-nitrobenzyl alcohol), 2-pentadecanone, (1R*,6S*,10R*)-5,5-dimethyl-11,12-dioxatricyclo[8.2.1.0(1,6)] tridecan-10-ol, Methyl linoleate, and 3-furanacetic acid, 4-hexyl-2,5-dihydro-2,5-dioxo-2,5-dioxo-2,5-dioxo-2,5-dioxo-2,5-dioxo-2,5-dioxo-2 (Gemantari et al. 2021). Remarkably, 2-carboxymethyl-3-N-hexyl-maleic anhydride exhibited the highest cytotoxicity against the Hela cell line, with an IC_{50} of 301.53 ± 11.34 g/mL, surpassing its effects on other cell lines.

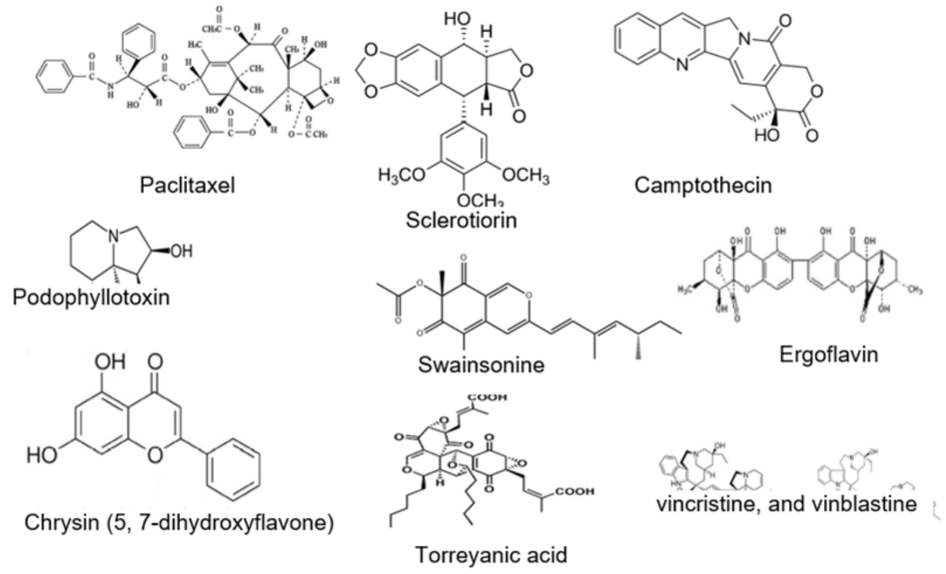


Figure 1. Anticancer Compounds Isolated from Endophytic Fungi (Ejaz et al. 2020).

Fungi Endophytes Produced Antidiabetic

Over the last decade, there has been a significant increase in diabetes prevalence, and will continue to rise in significance and quantity in the next future. As a result, screening for anti-diabetic benefits the novel and economical sources such as entophytes is required (Napitupulu 2018). Purified coumarone compound of 8-hydroxy-6,7-dimethoxy-3-methylisocoumarine obtained from the stem of *Quercus gilva* by endophytic fungi *Xylariaceae* sp. has considerable inhibitory effect against α-glycosidase (Indrianingsih & Tachibana 2017). Fungi *Colletotrichum* sp. from *Taxes sumatrana* cultivated in Indonesia produced the α-glycosidase inhibitor substances, include unsaturated fatty acids, specifically linolenic acids, linoleum, and oleic (Artanti et al. 2012). Others compounds that showed antidiabetic activity are quinadoline A (Strobel et al. 2004), scequinadoline J (Radjasa 2015), octadecanoic acid (Murugan et al. 2017), scequinadoline D (Čakar et al. 2018), peptide paecilodepsipeptide A (Glumac et al. 2017), asperpyridone A (Ancheeva et al. 2020), herbarin (Al-Hosni et al. 2020), aspergiamide A, and brevianamide K (Ye et al. 2021).

The diabetes has seen a significant increase over the past decade and is expected to continue rising in the future. Consequently, the search for novel and cost-effective sources with potential anti-diabetic properties, such as endophytes, is imperative (Napitupulu 2018). A purified coumarone compound, 8-hydroxy-6,7-dimethoxy-3-methylisocoumarine, derived from the stems of *Quercus gilva* via endophytic fungi *Xylariaceae* sp., has demonstrated a notable inhibitory effect against α-glycosidase (Indrianingsih & Tachibana 2017). *Colletotrichum* sp. from *Taxes sumatrana* cultivated in Indonesia has been found to produce α-glycosidase inhibitor substances, including unsaturated fatty acids such as linolenic acids, linoleic acid, and oleic acid (Artanti et al. 2012). Other compounds exhibiting anti-diabetic potential include quinadoline A (Strobel et al. 2004), scequinadoline J (Radjasa 2015), octadecanoic acid (Murugan et al. 2017), scequinadoline D (Čakar et al. 2018), peptide paecilodepsipeptide A (Glumac et al. 2017), asperpyridone A (Ancheeva et al. 2020), herbarin (Al-Hosni et al. 2020), aspergiamide A, and brevianamide K (Ye et al. 2021).

Antimicrobial Compounds Produced by Fungal Endophytes

Numerous endophytic fungi have been observed to synthesise alkaloids, flavonoids, peptides, phenols, polyketides, quinones, steroids, and terpenoids, which possess antibacterial properties (Mousa & Raizada 2013). Flavonoids are compounds generated by plants in response to microbial infections and exhibit hydroxylated phenolic characteristics. These antibacterial flavonoids display a diverse spectrum of activity against various cellular targets, facilitated through interactions such as hydrogen bonding, hydrophobic effects, and covalent bonding with proteins. Consequently, their antimicrobial activity is associated with the disruption of microbial adhesins, cell envelope transport proteins, enzymes, and other vital proteins. Furthermore, lipophilic flavonoids can influence microbial membranes (Cowan 1999; Mishra et al. 2009).

Endophytic fungi, specifically *Lasiodiplodia theobromae* and *Aspergillus oryzae* isolated from *Pometia pinnata* in Western Papua, have demonstrated inhibitory effects against *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (Setyaningsih et al. 2020). Endophytic fungi residing in the endemic plants of South Kalimantan's *Mangifera casturi* have produced antibacterial compounds, including di-n-octyl phthalate, benzyl alcohol, high-oleic safflower oil, benzene acetonitrile, and benzotriazole, which exhibited inhibitory effects on Methicillin Resistant *Staphylococcus aureus* (MRSA) with an MIC value of 1.56% (Nuraini 2023). A molecular docking study has indicated that endophytic fungi *Trichoderma* sp., isolated from *Caesalpinia sappan* wood in South Sulawesi, effectively inhibited *Mellasezia* sp. (Susanti et al. 2021). A compound named 3-acetyl -2,5,7-trihydroxy-1,4-naphtalenedione produced by endophytic fungi isolated from *Tinospora crispa* displayed superior inhibitory capabilities compared to commercial antimicrobials (chloramphenicol, cabisidin, and nystatin) against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* (Praptiwi et al. 2013). Indonesian medicinal plants' endophytic fungi exhibiting potential against pathogenic bacteria are summarised in Table 5.

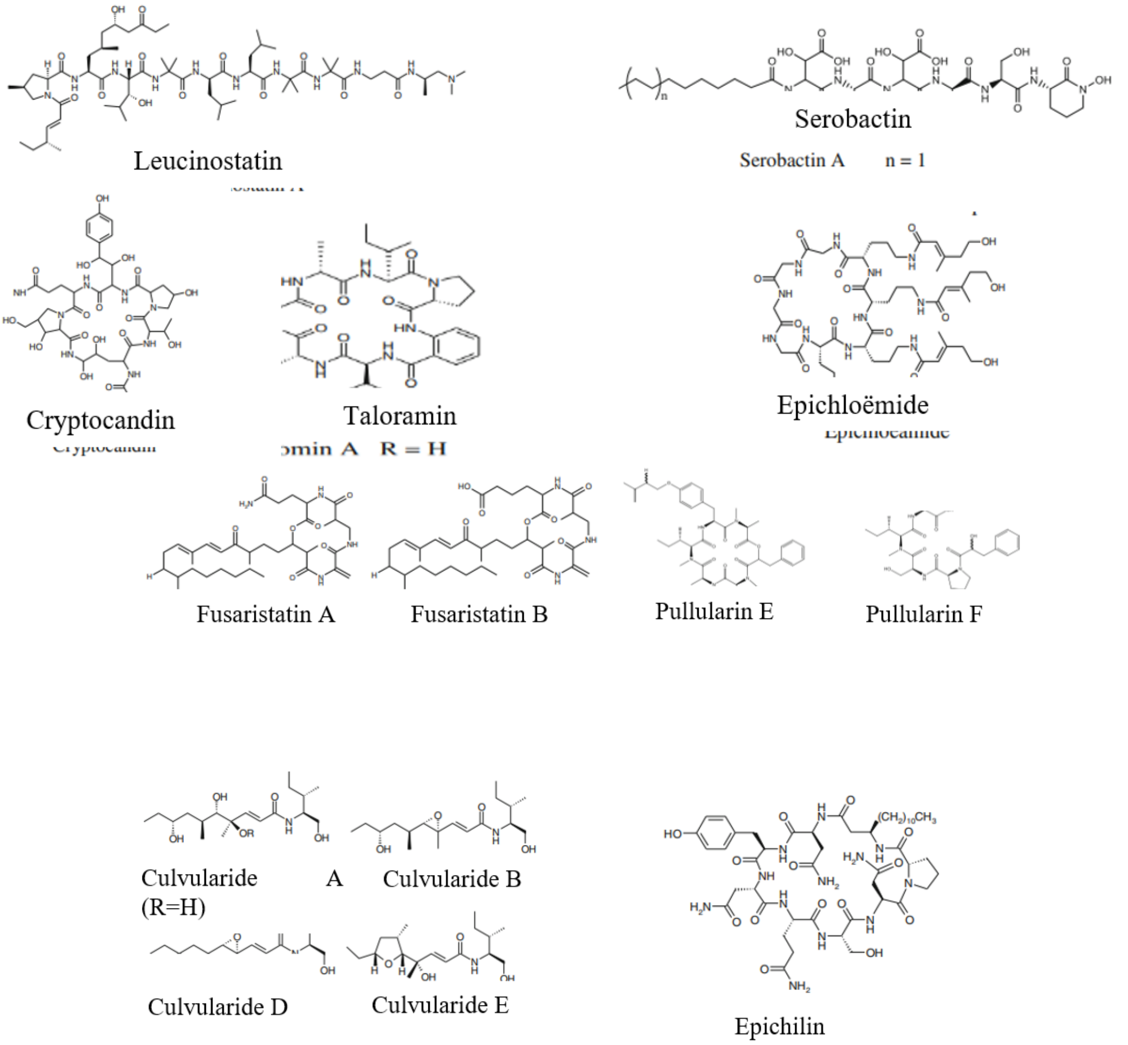
Table 5. Endophytic Fungi from Indonesian Medicinal Plants with Antimicrobial Potential.

Endophytic fungi	Host plants	Microorganism test	References
Trichoderma harzianum	*Zingiber officinale* Rosc.	*Staphylococcus aureus*	Harwoko et al. 2021
Neopestalotiopsis sp. and *Peniophora lycii*	*Rhizophora mucronata* Lamk.	*Eshcerichia coli* and *Staphylococcus aureus*	Fareza et al. 2018
Colletotrichum sp. and *Fusarium* sp.	*Physalis angulata* L.	*Eshcerichia coli* and *Staphylococcus aureus*	Palupi et al. 2021
Penicillium sp.	*Rhizophora apiculata* BI and *Bruguiera gymnorrhiza* (L.) Lamk.	*Salmonella typhi*	Rossiana et al. 2016
Cladosporium oxysporum	*Aglaia odorata* Lour	*Escherichia coli*, *Candida albicans*, and *Staphylococcus aureus*,	Sugijanto et al. 2016
Colletotrichum sp., *Penicillium* sp., *Trichophyton* sp., *Botrytis* sp., and *Trichophyton* sp.	*Medinilla speciosa* Blume	*Bacillus subtilis* and *Shigella dysenteriae*	Amelia et al. 2021
Culvularia lunata and Diaporthe phaseolorum	*Acanthus ilicifolius* L.	*Escherichia coli*, *Candida albicans*, *Staphylococcus aureus*, and *Shigella dysenteriae*	Widayanti et al. 2019

Table 5. Contd.

Endophytic fungi	**Host plants**	**Microorganism test**	**References**
Torulla sp., *Fusarium* sp., and *Drechcera* sp.	*Kaempferia galanga* L.	*Staphylococcus aureus,* *Vibrio cholera,* *Eschericia coli, and* *Bacillus subtilis*	Efendi et al. 2020
Aspergillus fumigatiaffnis	*Tribulus terestris* L.	*Streptococcus pneumoniae* and *Enterococcus faecalis*	Ola et al. 2018
Fusarium sp. and *Aspergillus* sp.	*Zingiber officinale* var. Roscoe	Methicillin Resistant *Staphylococcus aureus* (MRSA)	Sari et al. 2020

Antimicrobial peptides (AMPs) represent a class of broad-spectrum antimicrobials effective against bacteria, fungi, and viruses (Bahar & Ren 2013). These peptides play a crucial role in safeguarding various organisms, including humans, animals, and plants, by serving as the primary defense mechanism in the innate immune system (Lei et al. 2019). AMPs can be categorized based on their amino acid composition, structure, and function. They are generally classified into two groups: (1) linear, helical peptides devoid of cysteine, containing amino acids like glycine, proline, tryptophan, arginine, and histidine, exemplified by magainin and cecropin; and (2) cysteine-containing polypeptides characterized by disulfide bridge(s) formation, such as insect defensin (Bahar & Ren 2013; Moravej et al. 2018; Haney et al. 2019). Several AMP compounds produced by fungal endophytes, along with their chemical structures, are illustrated in Figure 2.



Leucinostatin

Serobactin

Cryptocandin

Taloramin

Epichloëmide

Fusaristatin A

Fusaristatin B

Pullularin E

Pullularin F

Culvularide A (R=H)

Culvularide B

Culvularide D

Culvularide E

Epichilin

Figure 2. Antimicrobial peptides (AMPs) synthesised by endophytic fungi with antimicrobial properties.

CONCLUSION

Traditional plant-based medicine has been an integral part of Indonesian culture, across the diverse archipelago. Exploring their potential medicinal properties through the use of endophytic microorganisms, particularly fungi in this context, emerges as a promising strategy to safeguard the preservation of these valuable plant species. Endophytic fungi hold great promise due to their ability to synthesize compounds similar to those produced by their host plants, alongside a spectrum of bioactivities relevant to various therapeutic applications. Many of Indonesian medicinal plants have been investigated, yielding endophytic fungi with demonstrated antioxidant properties, anticancer potential, antidiabetic compounds, and antibacterial activities. Consequently, these endophytic fungi associated with medicinal plants represent a wellspring of bioactive compounds with the potential to shape the future of Indonesian pharmaceuticals.

AUTHOR CONTRIBUTION

E.S., searched the literatures and wrote the manuscript, A.K., Z.D., H.N., H.K., A.A., and S.H.L supervised the processes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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