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A Review of Indonesia's Biodiversity as a Resource for Epigenetic Research: Opportunities and Future Directions

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Abstract: Indonesia, a megadiverse nation, possesses extraordinary biological wealth, including a vast array of medicinal plants, diverse fauna, and unique microbial ecosystems. This rich biodiversity, however, faces severe threats from habitat loss and climate change, underscoring the urgent need for its documentation and scientific utilization, particularly in emerging fields such as epigenetics. Epigenetics, which involves heritable changes in gene expression without altering the DNA sequence, is fundamental to understanding biological processes and disease. While foundational epigenetic discoveries often originate from microorganisms, Indonesia's extensive microbial and plant diversity, including endemic species, remains largely unexplored regarding its epigenetic potential. This review highlights Indonesia's biodiversity, including representative species, as a promising source of novel model organisms for epigenetic research and bioactive metabolites with significant medical potential, which may possess epigenetic-modulating properties as natural 'epidrugs' inspired by traditional Indonesian herbal medicine known as jamu. Bridging biodiversity research with molecular epigenetics offers a powerful framework for identifying new epigenetic mechanisms, regulators, and natural compounds, opening new frontiers in personalized medicine and disease prevention within Indonesia's unique biological and cultural landscape.

Keywords: Epidrugs; Epigenetics; Indigenous microbiota**;** Indonesian herbal medicine; Plant biodiversity

Introduction

Indonesia ranks among the world's most biodiverse nations, harboring the greatest number of indigenous medicinal plants after the Amazon rainforest. Approximately 10% of the world's flowering plant species, 12% of its mammals, 16% of its reptiles, and 17% of all bird species are distributed across Indonesia's vast archipelago of more than 17,000 islands, encompassing both terrestrial and marine ecosystems (Elfahmi et al. 2014; Rintelen et al., 2017; CBD Secretariat 2016). The archipelago's unique biogeographical position at the intersection of Asian and Australian continental shelves has fostered exceptional evolutionary processes, resulting in distinct ecological communities and novel biochemical pathways that remain largely unexplored (Lohman et al., 2011). Traditional Indonesian communities have long recognized and utilized this biological wealth, with extensive ethnobotanical knowledge systems documenting the medicinal properties of thousands of plant species across diverse ethnic groups (Syamsiah et al., 2016; Batubara & Prastya, 2020). However, rapid habitat loss, deforestation, and climate change pose significant threats to this irreplaceable biodiversity, underscoring the urgent need to document and utilize these resources for scientific advancement, particularly to support the development

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of emerging epigenetic studies, before they are lost forever (Riswan & Yamada, 2006; Sodhi et al., 2004).

Epigenetics has emerged as a pivotal field in modern biology, encompassing the study of heritable changes in gene expression that occur without alterations to the underlying DNA sequence (Bird, 2007; Louis, 2022; Grewal, 2023). The primary epigenetic mechanisms include DNA methylation, histone modifications (such as acetylation and methylation), and regulation by non-coding RNAs, all of which collectively orchestrate complex patterns of gene expression in response to environmental stimuli (Kouzarides, 2007; Frías-Lasserre & Villagra, 2017; Louis, 2022). These epigenetic modifications serve as molecular switches that can be dynamically regulated throughout an organism's lifetime, providing mechanisms for cellular adaptation to environmental changes and stress responses (Jaenisch & Bird, 2003). The reversible nature of epigenetic marks holds profound implications for therapeutic interventions, as these modifications can be influenced by diet, lifestyle, and pharmacological agents (Feinberg, 2007; Lorenzo et al., 2022; Dai et al., 2024).

Globally, the incidence of lifestyle-related diseases, including obesity, hypertension, type 2 diabetes, stroke, hypothyroidism, gout, and various cancers, continues to rise (Dalbeth et al., 2016; Sharma et al., 2009; Wang et al., 2017). Notably, conditions such as diabetes and cancer have been closely linked to epigenetic dysregulation (Ling & Rönn, 2019; Sharma et al., 2009). Consequently, a comprehensive understanding of epigenetic regulation has become increasingly vital across disciplines, ranging from developmental biology and evolutionary studies to disease pathogenesis and personalized medicine, firmly positioning epigenetics at the forefront of contemporary biological research.

Epigenetics plays a crucial role in orchestrating the dynamic organization of chromatin, influencing whether DNA is tightly packed (heterochromatin) or loosely arranged (euchromatin). This regulation directly impacts the accessibility of genes and, consequently, their transcriptional activity. Euchromatin represents transcriptionally active regions of the genome characterized by open chromatin, histone acetylation, and reduced DNA methylation, whereas heterochromatin consists of condensed, transcriptionally repressive domains marked by histone modifications such as H3K9me (histone H3 lysine 9 methylation). The interplay between these chromatin states is mediated through epigenetic modifications that establish and maintain gene expression patterns essential for cellular identity and genome stability (Goto & Nakayama, 2012; Wang et al., 2014; Blumenstiel, 2025). Recent studies have shown that epigenetic dysregulation can lead to abnormal transitions between euchromatin and heterochromatin, resulting in altered nuclear architecture and gene silencing, phenomena commonly observed in aging and cancer (Wang et al., 2024; Blumenstiel, 2025).

Early discoveries of key epigenetic enzymes, such as histone acetyltransferases (HATs) like Gcn5, histone deacetylases (HDACs) such as Rpd3, and NAD^+-dependent HDACs like Sir2, were first identified and extensively characterized in unicellular eukaryotes including *Saccharomyces cerevisiae* (budding yeast) and *Tetrahymena thermophila* (a ciliate protozoan) (Brownell et al., 1996; Imai et al., 2000; Kuo et al., 1996; Taunton et al., 1996). Building upon these foundational discoveries, exploration of novel microbial systems from diverse ecological niches offers new opportunities to uncover unconventional epigenetic-related protein regulators. In this context, Indonesia's remarkable microbial diversity, sustained by unique ecosystems ranging from tropical rainforests and mangroves to geothermal springs and deep-sea vents, represents an untapped reservoir of microorganisms with rare biochemical pathways and potential epigenetic relevance.

Research on the epigenetic mechanisms or regulators present in endemic or native Indonesian tropical plants, as well as in plant-derived natural products used in traditional jamu formulations, remains limited and fragmented. Furthermore, current plant biodiversity research in Indonesia has primarily focused on taxonomic classification, conservation efforts, and traditional ethnobotanical documentation (Sumadijaya et al., 2025; Rahayu et al., 2024). Progress towards detailed phytochemical characterization or mechanistic biological evaluation of plant natural products is relatively slow (Wirasisya et al., 2023). The existing body of research on Indonesian medicinal plants has identified numerous bioactive compounds with demonstrated pharmacological effects, with insufficient attention given to their potential in epigenetic-related disease medicine development (Hanif et al., 2025; Tailor et al., 2025; Zheng et al., 2025). Furthermore, the integration of traditional knowledge with modern epigenetic research methodologies remains underdeveloped, representing a missed opportunity to leverage centuries of accumulated wisdom about bioactive species.

Bridging biodiversity research with molecular epigenetics offers a powerful framework for identifying novel epigenetic mechanisms, regulators, and natural compounds capable of modulating gene expression through chromatin remodeling and related pathways. Harnessing this potential could open new frontiers in personalized medicine and disease prevention, particularly within Indonesia's unique biological and cultural landscape. Building on this perspective, the present review highlights Indonesia's rich microbial and plant biodiversity as a promising reservoir of both novel

model organisms for basic epigenetic studies and bioactive metabolites with potential epigenetic-modulating properties, including potential candidates for future epidrug (epigenetic drug) development inspired by traditional Indonesian herbal medicine known as jamu.

Method

This study employs a Systematic Literature Review (SLR) approach. SLR is a structured process designed to gather relevant evidence on a specific topic according to predefined eligibility criteria, with the aim of providing comprehensive answers to the formulated research questions (Mengist et al., 2020). The research process involved systematically collecting and analyzing scholarly publications related to the fundamental concepts and historical development of epigenetics, Indonesia's unique microbial and plant biodiversity, including endemic and native species, and natural bioactive compounds, without restrictions on publication year.

Result and Discussion

Epigenetics refers to the study of heritable changes in gene expression that occur without alterations in the DNA sequence, typically mediated by molecular mechanisms such as DNA methylation, histone modification, chromatin remodeling, and non-coding RNAs (Berger et al., 2009). This review primarily focuses on the fundamental concepts and historical development of epigenetics, as well as some studies on Indonesia's unique biodiversity as a rich reservoir for future epigenetic research and discovery. The conceptual diagram illustrates how Indonesia's rich biodiversity, encompassing diverse microbes and plants, including endemic and newly discovered native species, serves as a foundation for the discovery of unique metabolites and biochemical pathways (Figure 1).

Epigenetic Regulation

The term "epigenetics" was first coined by British developmental biologist Conrad Waddington in the 1940s to describe the process by which genotype gives rise to phenotype through developmental pathways (Waddington, 1942). Initially, the field was conceptual and focused on gene-environment interactions during development. However, with advancements in molecular biology in the late 20th century, epigenetics took on a more mechanistic dimension, referring to heritable changes in gene expression that do not involve alterations to the underlying DNA sequence. The field gained significant momentum in the 1990s and early 2000s with the identification of DNA methylation, histone modifications, and non-coding RNAs (ncRNAs) as molecular mediators of gene silencing and activation. Breakthroughs in Next Generation Sequencing (NGS) and chromatin immunoprecipitation techniques (ChIP-seq, Bisulfite-seq) further enabled high-resolution mapping of epigenomic landscapes across various species (Avramova, 2011; Seffer et al., 2013).

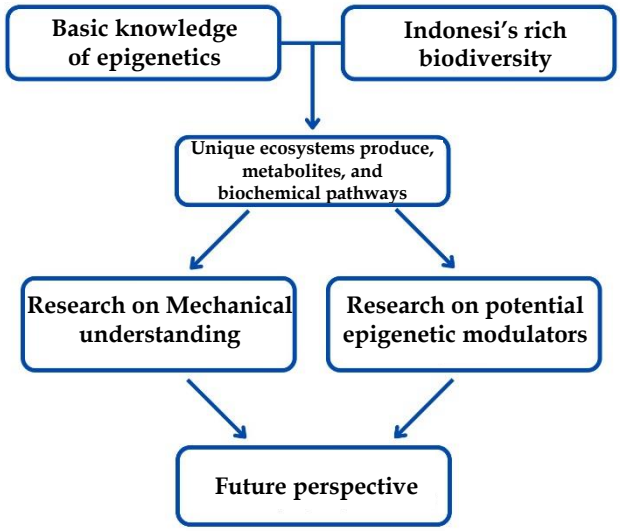

Figure 1. Conceptual framework linking Indonesia's biodiversity to epigenetic research and discovery

In plants, epigenetics has become an indispensable framework for understanding how plants adapt to environmental stress and regulate key processes such as development, flowering, and transposon silencing (Temel et al., 2015; Zilberman, 2008). Epigenetic mechanisms encompass several layers of gene regulation that do not involve changes to the DNA sequence, including DNA methylation, histone modifications, histone variants, and non-coding RNAs (ncRNAs) (Figure 2). These mechanisms play crucial roles in regulating chromatin structure, genome stability, and gene expression patterns during development, cellular differentiation, and also disease. Epigenetic modifications are not only reversible but in many cases heritable through mitosis and meiosis.

DNA Methylation

DNA methylation is one of the epigenetic modifications that is taxonomically restricted to certain groups, such as mammals and plants, and is rare or absent in many fungi (Colot & Rossignol, 1999). In mammals, DNA methylation primarily occurs at the 5th carbon of cytosine residues in CpG dinucleotides, catalyzed by a family of DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B (Dan & Chen, 2022). Approximately 60–80% of CpG sites

(CpG sites are regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence of bases) in the mammalian genome are methylated, a modification critical for gene regulation, development, and genome stability (Dan & Chen, 2016). Aberrant DNA methylation patterns are closely associated with disease, particularly cancer. In tumors, both global hypomethylation (leading to genomic instability) and promoter hypermethylation (leading to silencing of tumor suppressor genes) are commonly observed (Baylin et al., 2001; Jin et al., 2011). Methylated DNA can block transcription factor binding directly or recruit methyl-CpG-binding domain (MBD) proteins, which in turn recruit repressive chromatin-modifying complexes (Robertson, 2005). Thus, DNA methylation is not only a silencing signal but also functions in coordination with other epigenetic modifications to shape chromatin architecture.

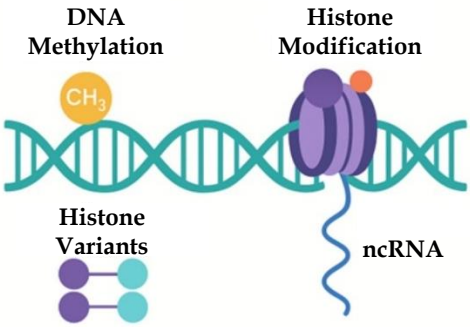

Figure 2. Epigenetic mechanisms involve multiple layers of gene regulation, including DNA methylation, histone modification, histone variants, and non-coding RNAs (ncRNAs). These modifications influence chromatin structure and gene expression without altering the underlying DNA sequence

Histone Modifications

Histone modifications represent another essential layer of epigenetic control. These post-translational modifications (PTMs) occur primarily on the N-terminal tails of histone proteins but can also affect residues within the globular core domain. Key types of histone modifications include acetylation, methylation, phosphorylation, ubiquitination, and sumoylation, each influencing chromatin structure and gene accessibility in different ways (Bannister & Kouzarides, 2011). The discovery of histone acetyltransferase (HAT) activity in *T. thermophila* by David Allis and colleagues in 1996 marked a pivotal moment in chromatin biology. They identified a 55-kDa nuclear protein with HAT activity, later shown to be orthologous to Gcn5, a known transcriptional regulator in *S. cerevisiae*. This provided direct evidence linking histone acetylation to gene activation (Brownell et al., 1996; Kuo et al., 1996; Verdin & Ott, 2015).

In contrast, histone methylation is often associated with gene repression and heterochromatin formation, though its effect depends on the residue and degree of methylation. This modification is highly conserved across species, from yeast to humans, and is catalyzed by histone methyltransferases (HMTs). Histone methylation was once thought to be irreversible. However, the discovery of histone demethylases (enzymes that remove methyl groups from lysine or arginine residues on histone proteins) has demonstrated that methylation at key sites on histone H3 and H4 tails, specifically H3K4, H3K9, H3K27, and H3K36, is dynamically regulated (Fei & Yang, 2009). Histone phosphorylation, typically mediated by ATP-dependent kinases, adds a negative charge to histone tails, leading to changes in chromatin compaction and participating in DNA damage responses, cell cycle progression, and transcription regulation. Histone ubiquitination, involving the covalent attachment of ubiquitin, a 76-amino-acid polypeptide, is mediated through a cascade of enzymes: E1-activating, E2-conjugating, and E3-ligating enzymes. Ubiquitination of histones H2A and H2B is among the most studied, and is implicated in both transcriptional silencing and the DNA damage response (Bannister & Kouzarides, 2011; Uckelmann & Sixma, 2017). Sumoylation (small ubiquitin-like modifier conjugation) is a modification similar to ubiquitination, also involving E1, E2, and E3 enzymes. Histone sumoylation is generally associated with transcriptional repression. In *S. cerevisiae*, sumoylation is enriched in subtelomeric regions, which are typically silenced and depleted of acetylation marks. However, emerging evidence suggests that sumoylation may also regulate actively transcribed genes, pointing to a more nuanced role in chromatin dynamics (Nathan et al., 2006; Wotton et al., 2017).

Histone Variants

In addition to post-translational modifications, histone variants contribute significantly to chromatin diversity and epigenetic regulation. Unlike canonical histones, which are synthesized and incorporated during DNA replication (S-phase), histone variants are expressed and deposited into chromatin independently of replication, often in response to cellular stress or developmental cues (Henikoff & Smith, 2015). Histone variants can replace standard histones in nucleosomes, altering chromatin structure and function. For instance, H2A.Z and H3.3 are associated with gene activation and regulatory regions, while macroH2A and H2A.X are implicated in gene silencing and DNA damage response, respectively (Talbert & Henikoff, 2016). The deposition of histone variants is tightly regulated by specific histone

chaperones and ATP-dependent chromatin remodeling complexes, such as HIRA for H3.3 and Chz1/SWR1 for H2A.Z (Banaszynski et al., 2010). These variants influence chromatin accessibility, nucleosome stability, and the recruitment of transcription factors or repair proteins. Importantly, dysregulation of histone variant expression or incorporation has been linked to developmental disorders and cancer, highlighting their role in epigenome maintenance (Elsässer et al., 2011).

Non-coding RNAs (ncRNAs)

Non-coding RNAs (ncRNAs) are a broad class of RNA molecules that are not translated into proteins but play critical roles in epigenetic regulation. They are generally categorized into small ncRNAs (e.g., microRNAs, piRNAs) and long non-coding RNAs (lncRNAs) based on size. lncRNAs, which are more than 200 nucleotides in length, can act as scaffolds, guides, decoys, or signals for chromatin-modifying complexes (Marchese et al., 2017). A well-studied example is Xist, a lncRNA essential for X-chromosome inactivation in female mammals. Xist recruits Polycomb repressive complexes (PRC1 and PRC2) to the X chromosome, initiating gene silencing and heterochromatin formation (Engreitz et al., 2013). Small ncRNAs, such as siRNAs and piRNAs, are also involved in heterochromatin assembly and transposon silencing, particularly in model organisms like *S. pombe* and *Drosophila melanogaster*. In fission yeast, for example, RNA interference (RNAi)-dependent pathways use siRNAs to guide the Clr4 histone methyltransferase to specific genomic loci, leading to H3K9 methylation and heterochromatin formation (Goto & Nakayama, 2012; Martienssen & Moazed, 2015). Overall, ncRNAs provide sequence specificity to epigenetic processes and can coordinate with DNA methylation and histone modifications to regulate gene expression across a wide range of biological contexts.

Epigenetic Early Discoveries in Different Microorganisms: Foundational Insights

The field of epigenetics is often associated with complex multicellular organisms, several foundational discoveries emerged from studies in microorganisms, particularly bacteria, yeast, and protozoa. These systems provided crucial insights into the molecular machinery of epigenetic regulation, owing to their genetic tractability and simplicity. In the 1990s, research in *S. cerevisiae* demonstrated that telomeric position-effect variegation (TPE) could silence gene expression in a heritable but reversible manner, without altering DNA sequence. This phenomenon was mediated by Silencer- or telomere-binding proteins that subsequently recruit the SIR (Silent Information Regulator) complex, particularly Sir2, which deacetylates H4K16 for efficient recruitment of the SIR complex to silencer and promote chromatin compaction and transcriptional repression (Gottschling et al., 1990; Moazed, 2011; Gartenberg & Smith, 2016).

Further advances came from the ciliate *T. thermophila* in 1996, with the first discovery of nuclear HAT and later on served as a model for chromatin remodeling and DNA elimination. This organism exhibits programmed genomic rearrangements during macronuclear development, driven by histone acetylation and small RNA-mediated chromatin remodeling, revealing complex layers of epigenetic programming in protozoa (Brownell et al., 1996; Chalker et al., 2013). Later on, the findings of HDAC in *S. cerevisiae*, and HP1 (heterochromatin protein 1) proteins that play important role in heterochromatin silencing in *S. pombe*, contribute to the epigenetic field development (Lachner, 2001). Collectively, these microbial studies provided essential early evidence for epigenetic inheritance, highlighting the roles of DNA methylation, histone modification, and RNA-guided chromatin regulation in organisms far removed from humans. Despite Indonesia's extensive collection of microbial isolates from diverse habitats, research utilizing indigenous microorganisms or novel microbial species from Indonesia to investigate epigenetic mechanisms remains largely unexplored, particularly for those originating from unique environments such as tropical rainforests, geothermal springs, and deep-sea vents. In addition, Indonesia's exceptional plant biodiversity, including its endemic and native species, also represents a valuable resource that may harbor unique biochemical pathways and metabolites with significant scientific potential in epigenetic studies.

Perspective on Indonesia's Microbial Diversity as a Frontier for Epigenetic Research

Indonesia, the world's largest tropical island nation, is one of 17 officially recognized megadiverse countries. The nation is also home to rich agrobiodiversity, encompassing diverse cultivars and domesticated livestock. Conservation efforts are supported by 566 protected areas, including 43 terrestrial national parks, 239 nature reserves, and extensive marine protected zones covering over 4.5 million hectares. Indonesia's tropical forests, particularly the lowland rainforests, span more than 88 million hectares and are a major reservoir of biological and microbial diversity (Ministry of Forestry, 2011).

Due to its unique nature, Indonesia is among the world's most biologically diverse nations, yet the epigenetic potential of its microbial eukaryotes, particularly yeasts and protists originally isolated from Indonesia's unique landscape, remains vastly understudied. These microorganisms are critical to

chromatin biology, as they may harbor unique biochemical machinery underlying epigenetic regulation. However, while model organisms such as *S. cerevisiae*, *S. pombe*, and *T. thermophila* have illuminated many core epigenetic processes as discussed earlier, there is growing recognition that novel lineages, particularly from underexplored tropical ecosystems, geothermal springs, and deep-sea vents, may harbor distinct chromatin regulatory systems with unrecognized potential.

Indonesia's yeast biodiversity presents a compelling opportunity for exploration in the context of epigenetic research. A comprehensive study by Sjamsuridzal et al. (2010) successfully isolated 2,147 yeast strains from 315 environmental samples collected across Java, Sumatra, Sulawesi, Lombok, and Timor. Through analysis of the Internal Transcribed Spacer (ITS) region and large-subunit rDNA, the researchers identified 306 known species and over 209 potentially novel taxa. Remarkably, more than 41% of the isolates could not be matched to any previously described species, revealing a vast, untapped microbial gene pool within Indonesia's forests, soils, and aquatic ecosystems. More recently, novel yeast species such as *Citeromyces cibodasensis* and *Rhodotorula tropicalis* were isolated from leaf litter in Indonesia, while *Metschnikowia cibodasensis* was discovered from flowers in the Cibodas Botanical Garden, West Java (Sjamsuridzal et al., 2013; Kanti et al., 2018; Khunnamwong et al., 2025). These newly identified yeasts may harbor divergent histone variants, chromatin-modifying enzymes, or unique secondary metabolites that could play key roles in epigenetic regulation and chromatin dynamics.

Protists also show high cryptic diversity across Indonesia's freshwater and marine habitats, offering another frontier for epigenetic research. A metabarcoding study in Lake Balekambang, Dieng Plateau, Central Java, revealed 48 amplicon sequence variants (ASVs) of protozoa from sediment samples, spanning Tritrichomonadidae, Ophryoscolecidae, Gregarinidae, Cyrtolophosididae, Hexamitidae, Isotrichidae, Oxytrichidae, Vannellidae, Vermamoebidae, and other unidentified Eukaryota taxa (Nabila et al., 2024). Some of the most striking discoveries in Indonesia come from diatom communities in lakes in Bali and Sulawesi have led to the description of new species such as *Achnanthidium bratanense* and *Encyonopsis indonesica* (Kapustin et al., 2021; Kapustin et al., 2022). As photosynthetic protists, these taxa often exhibit tightly regulated chromatin structures to manage environmental fluctuation, and thus provide unique models for understanding chromatin–environment interactions in extremophilic or oligotrophic conditions.

In conclusion, Indonesia's yeast and protist communities, especially those harboring novel species, offer transformative potential for epigenetic research. Harnessing this diversity may not only expand the repertoire of model organisms, but also uncover lineage-specific mechanisms of epigenetic regulation that remain invisible in conventional laboratory model organisms. Future directions should focus on systematic bioprospecting across Indonesian ecosystems, such as lowland forests, mangroves, geothermal springs, traditional fermented foods, and animal microbiomes, to isolate, characterize, and genetically profile microbial taxa for their potential in chromatin biology. Genome mining, multi-omics integration, and functional epigenetic assays should be employed to screen for regulatory proteins and unique regulatory mechanisms that could accelerate discovery in epigenetics.

Indonesia's Plant Diversity as a Frontier for Epigenetic Research

Indonesia is one of the most botanically diverse countries in the world, with 30,466 native species of vascular plants, representing approximately 8.7% of global vascular plant richness. Among these, around 27,824 are angiosperms, including approximately 28,000 flowering plant species, many of which are endemic to the region, particularly within major phytogeographic zones such as Sundaland, Wallacea, and Papua (Sun et al., 2024). This extraordinary diversity, spanning a wide range of ecosystems, from mangrove forests and peat swamps to volcanic highlands and montane habitats, remains largely underexploited for plant epigenetic research (Sun et al., 2024).

While most plant epigenetic studies have focused on model organisms such as *Arabidopsis thaliana*, rice, and maize, non-model species from ecologically diverse regions, such as Indonesia, have the potential to reveal novel epigenetic adaptations and regulatory mechanisms not captured in traditional systems (Richards et al., 2017). In extreme environments such as Indonesia's mangroves and peat swamps, plants are exposed to salinity, hypoxia, and nutrient limitation. Evidence from tropical mangrove species demonstrates that such stresses induce convergent gene body methylation (gbM), which contributes to transcriptional robustness under chronic saline stress. In three independently evolved mangrove taxa (*Avicennia marina, Rhizophora apiculata,* and *Sonneratia alba*), de novo gbM was convergently acquired since divergence from their non-mangrove relatives, facilitating long-term stress adaptation of mangroves in the face of a severe reduction in genetic diversity (Wang et al., 2021). Similarly, the mangrove *Bruguiera gymnorhiza* shows salinity-induced, genome-wide DNA methylation changes, especially CG and non-CG hypermethylation in transposable elements, that associate with habitat-

specific expression patterns between the samples grown in saline and brackish water (Miryeganeh et al., 2022).

The published findings demonstrate the strong potential for conducting epigenetic studies in Indonesia's mangrove and peat swamp ecosystems, highlighting that tropical megadiverse systems remain critically underrepresented in global epigenetics literature (Richards et al., 2017). For instance, several endangered and near-threatened mangrove species in Indonesia, such as *Bruguiera hainesii*, *Scyphiphora hydrophyllacea*, *Camptostemon philippinensis*, and *Ceriops decandra* (Table 1), represent valuable yet vulnerable genetic resources. Conducting comprehensive epigenomic profiling of these limited species will be valuable not only for understanding their adaptive responses and the vast diversity of their epigenetic machinery but also for guiding conservation and preservation strategies through molecular insights.

In addition, Indonesia harbors numerous native and endemic plant species, some of which grow exclusively in restricted regions and cannot be cultivated elsewhere. Some examples of these plants include *Anaphalis javanica* (Javanese edelweiss), *Rafflesia arnoldii* (giant corpse flower), *Myristica fragrans*, and *Aglaonema* spp. (Table 2). *A. javanica* is a herbaceous and woody flowering plant, recognized as a pioneer species that commonly thrives in volcanic ash deposits. It typically grows in alpine zones at elevations between 1,600–3,600 meters above sea level, where temperatures range from 5°C to 25°C (Steenis, 2010; Amalia et al., 2019; Rozianty & Wijaya, 2019). Despite ongoing conservation efforts, this species remains endangered, and no epigenomic profile has not yet been reported. Meanwhile, *R. arnoldii*, an endemic species in Indonesia belonging to the Rafflesiaceae family (Asiandu, 2021), is classified as vulnerable and represents an obligate parasitic plant notable for its exceptionally large flowers that emit an odor similar to decaying flesh, as an evolutionary adaptation that attracts specific pollinators (Kusuma et al., 2018; Samidjo et al., 2021; Bascos et al., 2024). This striking pollination mechanism likely reflects a form of natural selection, where the plants evolved to attract specific pollinators. However, the epigenetic basis underlying this adaptation also remains unexplored.

M. fragrans (nutmeg) is a valuable plant widely utilized in the pharmaceutical, spice, and cosmetics industries worldwide. It is indigenous to the Maluku Islands, with the largest production in Indonesia located on Sangihe Island, North Sulawesi (Agustina et al., 2024). Nutmeg has been reported to possess multiple pharmacological properties, including aphrodisiac, stomachic, carminative, tonic, nervous stimulant, aromatic, narcotic, astringent, hypolipidemic, antithrombotic, antifungal, antidysenteric, and anti-inflammatory activities (Tajuddin et al., 2005). Despite its broad range of health benefits and the high economic value of its essential oils, molecular and epigenetic studies on this important plant remain limited.

Similarly, *Aglaonema* spp., widely cultivated as ornamental plants throughout Indonesia, exhibit remarkable species and cultivar diversity. Beyond their aesthetic value, these plants play roles in environmental pollution control and possess potential medicinal properties (Akbar et al., 2021). The importance of epigenetics in plant cultivation and breeding has grown rapidly in recent years, as epigenetic mechanisms enable the development of new varieties through phenotypic modification without altering DNA sequences, thereby avoiding classification as genetically modified organisms (Kisvarga et al., 2025). This underscores the urgent need for epigenetic research in ornamental plants, particularly in *Aglaonema* spp., where such studies have yet to be conducted. The plants listed above represent only a few of Indonesia's many native and endemic species, most of which have not yet been studied in terms of epigenomic profiling or other epigenetic-related aspects.

Bioactive Compounds from Indonesia's Microbial and Herbal Medicine for Epigenetic-Related Disease

Indonesia's rich herbal heritage offers a valuable foundation for the discovery of bioactive compounds capable of modulating epigenetic mechanisms implicated in diseases such as cancer, and diabetes. For example, bioactive compound like curcumin, derived from *Curcuma longa,* a plant widely used for jamu formulation, have been shown to inhibit DNA methyltransferase (DNMT1) inducing hypomethylation in cancer cells, in which in vitro and in vivo treatment with hypomethylating agents has proven to be effective in restoring gene expression and normal patterns of differentiation and apoptosis in malignant cells (Liu et al., 2009). Similarly, flavonoids such as apigenin and rosmarinic acid exhibit chemopreventive activity in in vitro, in vivo, and in silico studies, offering potential as adjuncts in cancer therapy (Abutayeh et al., 2024). Exploring Indonesia's diverse medicinal flora through an epigenetic lens may thus lead to the identification of novel natural epidrugs, integrating traditional medicine with molecular therapeutics for precision health.

Beyond cancer therapy, epidrugs hold promise for metabolic and neurological diseases, and even in regenerative medicine (Altucci & Rots, 2016). Current epidrugs approved by FDA are chemically synthesized. However, some of them are actually firstly isolated from bacterium, such as romidepsin and 5-azacytidine. Romidepsin is also known by its trade name Istodax® (FR901228 or FK228), is a bicyclic depsipeptide first isolated in culture broths of *Chromobacterium violaceum*, a Gram-negative soil bacterium, based on its ability to

induce differentiation in transformed NIH 3T3 cells (Harrison et al., 2012). This natural product functions as a histone deacetylase (HDAC) inhibitor, predominantly targeting class I HDACs (e.g., HDAC1 and HDAC2) with nanomolar potency. 5-Azacytidine with trade name Vidaza, a DNMT inhibitor, can be isolated from bacterium *Streptoverticillium ladakanus* (Cihák, 1974). The discovery of romidepsin and 5-azacytidine thus underscores the potential of exploring Indonesia's rich microbial and plant biodiversity as a source of novel bioactive compounds with epigenetic-modulating activity.

Table 1. Summary of Indonesian Mangrove Species with Potential as Models for Epigenetic Studies

Species name	International Union for Conservation of Nature (IUCN) status	Distribution	Reference
Scyphiphora hydrophyllacea	Endangered	Tingki-tingki Village and Uwedikan Village of Banggai, Central Sulawesi	Utina et al. (2019)
Camptostemon philippinensis	Endangered	Balikpapan Bay, East Kalimantan	Sitepu et al. (2024)
Ceriops decandra	Near Threatened	Maleo Village, Paguat, Pohuwato District, Gorontalo	Umadji et al. (2023)
Bruguiera hainesii	Critically Endangered	Sungai Nibung is one of the coastal areas in Kubu Raya Regency, West Kalimantan	Safitri et al. (2024)

Table 2. Summary of Representative Indonesia-Originated and Endemic Plants with Potential for Epigenetic Studies

Species name	International Union for Conservation of Nature (IUCN) status	Distribution	Reference
Anaphalis javanica	Endangered	Mt. Papandayan, Mt. Semeru, Mt. Buni Telong Bener Meriah	Amalia et al. (2019)
Rafflesia arnoldii	Endangered	Meru Betiri National Park, tropical forests on the island of Sumatra, Kerinci Seblat National Park, Bukit Barisan Selatan National Park, Seblat Elephant Training Center in North Bengkulu, and Padang Guci, Kaur Regency in Bengkulu	Samidjo et al. (2022)
Myristica fragrans	-	Maluku and Sangihe island	Agustina et al. (2024)
Aglaonema spp.	-	Widely distributed	Akbar (2021)

A well-studied Indonesian medicinal plant is kencur (*Kaempferia galanga* L.), which contains several bioactive compounds such as luteolin and apigenin (Mustafa et al., 2010). *K. galanga* also produces ethyl p-methoxycinnamate (EMC) as its primary active compound. Recent studies have shown that EMC inhibits the proliferation of Ehrlich ascites tumor cells (EATC) by reducing intracellular ATP levels through the suppression of de novo fatty acid synthesis (Sasaki et al., 2025). However, the potential of EMC and other bioactive compounds derived from *K. galanga* to modulate chromatin regulation remains poorly studied.

Table 3. Indonesian Medicinal Plants Commonly Used in Jamu Formulations with Potential for Epidrug Studies

Plants	Local name	Known Biological Activities	References
Kaempferia galanga L.	Kencur	Antioxidant, anticancer	Mustafa et al. (2010); Sasaki et al. (2025)
Curcuma xanthorrhiza Roxb.	Temulawak	antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic, skincare and hepatoprotective properties	Rahmat et al. (2021)
Myrmecodia pendans	Ant nest plant/ sarang semut	Antidiabetic, anticancer, antibacterial	Putra et al. (2020); Primasari et al. (2022)
Spatholobus littoralis Hassk.	Bajakah	Anti-hypertension (under investigation), antigout	Abidin et al. (2024); Sianipar et al. (2024)

Another example of a plant commonly used as a component of jamu is *Curcuma xanthorrhiza* Roxb. *C. xanthorrhiza*, locally known as temulawak, contains more than 40 active compounds, including terpenoids, curcuminoids, and other phenolic constituents (Rahmat et al., 2021). *Myrmecodia pendans*, or traditionally known as ant nest fruit, is one of popular traditional medicines in Indonesia with a wide range of effects such as

antidiabetic, anticancer, antibacterial and free-radical scavenging agents (Putra et al., 2020; Primasari et al., 2022). *Spatholobus littoralis* Hassk., known locally as bajakah root, is currently being extensively researched and utilized as a medicinal plant by Indonesians. It is a typical plant found in West Kalimantan (Abidin et al., 2024). Traditionally, bajakah root has been used to treat gout and hypertension. LC MS/MS analysis of bajakah root has revealed that it contains primarily phenolic acids, flavonoids (isoflavones), and fatty acids (Sianipar et al., 2024). These representative Indonesian medicinal plants have been widely used in jamu formulations, and their potential as epidrugs has not yet been explored in detail. However, many remain understudied due to limited scientific investigation or their traditional use being confined to specific regions (Table 3).

Microbial-derived metabolites, such as those that led to the discovery of romidepsin and 5-azacytidine, are also crucial targets for investigation, not only plant-derived compounds. Unfortunately, comprehensive studies aimed at uncovering novel or functionally enriched microbial metabolites in Indonesia remain limited. Most current research focuses primarily on phenotypic characterization (e.g., antibacterial, anti-inflammatory, or antifungal activity) without thoroughly identifying the specific underlying bioactive compounds. One notable exception is the work on *Streptomyces* sp. GMR22, an actinobacterium isolated from the rhizosphere of eucalypt stands in Wanagama Forest, Yogyakarta (Islamiati et al., 2022), and *Ganoderma boninense* Pat., a soil fungus obtained from a healthy oil palm plantation in Indonesia (Lutfia & Rupaedah, 2025). Both studies profiled the metabolite components that may play key roles as biofungicidal agents. Although phenotypic assays show that both *Streptomyces* sp. and *G. boninense* possess promising biofungicidal properties, it remains unknown whether any of their metabolites may also function as epigenetic modulators, as no such investigations have yet been conducted.

Taken together, these findings highlight the vast yet underexplored potential of Indonesia’s medicinal plants and microbial resources as reservoirs of natural-product-derived epigenetic modulators. Advancing research in this direction will not only deepen molecular understanding of Indonesia’s traditional medicinal resources but may also lead to the discovery of novel epidrugs, offering new therapeutic avenues for epigenetic-related disease. Therefore, systematic bioprospecting and integrated multi-omics approaches are urgently needed to unlock the epigenetic potential embedded within Indonesia’s rich biological heritage.

Conclusion

Indonesia's unparalleled biodiversity, encompassing a vast array of microbial and plant species across diverse ecosystems, represents a largely untapped frontier for epigenetic research. This review underscores the critical need to leverage this biological richness to uncover unique epigenetic mechanisms, regulators, and novel bioactive compounds. While foundational epigenetic insights have emerged from model organisms, the unique evolutionary pressures and ecological niches within Indonesia's tropical rainforests, mangroves, geothermal springs, and deep-sea vents, suggest the presence of distinct chromatin regulatory systems and metabolites that have yet to be discovered. The potential of Indonesian yeast and protist communities, particularly those harboring novel species, to expand the repertoire of model organisms and reveal lineage-specific epigenetic regulation is immense. Similarly, the country's plant diversity, including endemic and endangered species, offers unique opportunities to study epigenetic adaptations to extreme environments and identify natural epidrugs. The current underrepresentation of tropical megadiverse systems in global epigenetics literature highlights a significant knowledge gap. Future research should prioritize systematic bioprospecting across Indonesian ecosystems, employing advanced techniques such as genome mining, multi-omics integration, and functional epigenetic assays. This comprehensive approach will facilitate the identification and characterization of novel regulatory enzymes, cofactors, and unique epigenetic mechanisms. Furthermore, integrating traditional ethnobotanical knowledge with modern epigenetic methodologies can accelerate the discovery of bioactive compounds with therapeutic potential. By bridging biodiversity research with molecular epigenetics, Indonesia can not only contribute significantly to global scientific advancement but also develop personalized medicine and disease prevention strategies tailored to its unique biological and cultural context. This endeavor is crucial not only for scientific discovery but also for informing conservation efforts and ensuring the sustainable utilization of Indonesia's invaluable natural heritage before it is irrevocably lost.

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The author declares no conflict of interest.

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