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# Bioactive Potential of Endophytic Fungi from the Genus *Aspergillus*: A Comprehensive Review of Secondary Metabolites and Their Biological Activities

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**ABSTRACT**

This review provides a comprehensive synthesis of current knowledge on the bioactive potential of endophytic fungi belonging to the genus *Aspergillus*, emphasizing their secondary metabolites and associated biological activities. A systematic literature search was conducted across major scientific databases, including Scopus, Web of Science, PubMed, ScienceDirect, and Google Scholar, covering publications from January 2020 to October 2025. Studies were selected based on inclusion criteria focusing on the isolation, metabolite characterization, and bioactivity evaluation of endophytic *Aspergillus* species. Relevant data on fungal species, host plants, metabolite classes, and biological functions were extracted, organized, and analyzed qualitatively using a thematic and comparative approach. The analysis revealed that *Aspergillus* species are prolific producers of diverse secondary metabolites such as alkaloids, polyketides, terpenoids, xanthones, and peptides, exhibiting a broad range of biological activities including antimicrobial, antioxidant, anticancer, anti-inflammatory, antifungal, and antiparasitic effects. Key compounds such as gliotoxin, terrein, and vitexin demonstrate strong pharmacological properties and highlight the genus's biotechnological significance. Overall, endophytic *Aspergillus* species represent an underexploited reservoir of natural bioactive compounds with high pharmaceutical and industrial relevance. Future research integrating genomics, metabolomics, and bioengineering is essential to unlock their full biosynthetic potential and advance sustainable drug discovery.

Keywords: *Endophytic Fungi, Genus Aspergillus, Secondary Metabolites, Biological Activities*

## I. INTRODUCTION

Endophytic fungi have gained significant scientific attention over the past two decades due to their remarkable ability to produce diverse secondary metabolites with potent biological activities (Munshi et al., 2022). These symbiotic microorganisms inhabit the internal tissues of plants without causing any apparent harm to their hosts. Within this mutualistic relationship, endophytes often synthesize bioactive compounds that are structurally similar or even identical to those produced by their host plants (Wen et al., 2023). Such metabolites include alkaloids, terpenoids, polyketides, phenolics, and peptides many of which exhibit strong antimicrobial, anticancer, antioxidant, and anti-inflammatory properties (Elghaffar et al., 2022).

The Aspergillus genus is one of the oldest known fungal genera. Its species can survive in extremely difficult environmental conditions and can affect plants, animals, and human health due to their pathogenic characteristics (Ibrahim et al., 2025). The genus *Aspergillus* encompasses more than 300 recognized species that occupy diverse ecological niches, ranging

from soil and decaying matter to marine environments and plant tissues (Greeff-Laubscher et al., 2020). Many of these species have been identified as prolific producers of secondary metabolites exhibiting a broad spectrum of biological activities. A new phenylacetic acid, methoxy-graphislactones C, a new anthraquinone (1 ′ E)-6,8-di-O-methyl averanti, a new phenanthrene derivative, 12-methyl entonaemin A and five previously reported compounds were isolated from the fermented extracts of the mangrove endophytic fungus *Aspergillus* sp. HMGh1–1 (Li et al., 2025).

In the context of endophytic lifestyles, *Aspergillus* species have been isolated from an extensive variety of plants distributed across different biogeographical regions (Zakaria, 2024). These include hosts belonging to genera such as Curcuma, Andrographis, Tinospora, Eurycoma, and Azadirachta, which are well known in traditional medicine for their pharmacological properties. The endophytic strains of *Aspergillus* associated with such medicinal plants often produce secondary metabolites that mirror or even enhance the therapeutic potential of their hosts, suggesting a possible co-evolutionary relationship in metabolite biosynthesis (Ibrahim et al., 2025).

This symbiotic association between *Aspergillus* endophytes and their host plants represents an ecologically and biochemically rich system, capable of generating novel molecular scaffolds and bioactive compounds (Zakaria, 2024). Furthermore, advances in fermentation technology, co-culturing strategies, and omics-based approaches (genomics, transcriptomics, and metabolomics) have begun to uncover the immense, previously untapped biosynthetic capacity of endophytic *Aspergillus*. Such developments open promising avenues for the discovery of new drugs, agrochemicals, and industrially relevant biomolecules. Consequently, a comprehensive review of the bioactive potential of endophytic *Aspergillus* species is essential to consolidate existing knowledge, identify novel trends, and guide future research toward sustainable exploitation of this prolific fungal genus in biotechnology and pharmaceutical innovation (Hagag et al., 2022).

Despite the growing body of literature on endophytic fungi, comprehensive reviews specifically focusing on the secondary metabolites and bioactivities of endophytic *Aspergillus* species remain limited. Most existing studies are fragmented, addressing individual strains or specific biological activities, without an integrated understanding of their chemical diversity, mechanisms of action, and pharmacological relevance (Zakariyah et al., 2024). Moreover, advances in metabolomics, genomics, and bioinformatics have revealed that many biosynthetic gene clusters in *Aspergillus* remain cryptic or silent under standard culture conditions, suggesting that the metabolic potential of this genus is far from fully explored (Adebayo et al., 2021).

Therefore, this review aims to provide a comprehensive synthesis of current knowledge regarding the secondary metabolites produced by endophytic *Aspergillus* species and their reported biological activities. By summarizing recent findings, identifying research gaps, and highlighting future perspectives, this article seeks to underscore the biotechnological significance of *Aspergillus* endophytes as promising sources of novel bioactive natural products for pharmaceutical and industrial applications.

## II. METHODS

### Literature Search Strategy (Modification (Alzahrani, 2025))

A comprehensive literature search was conducted to collect scientific publications related to endophytic fungi of the genus *Aspergillus*, their secondary metabolites, and associated biological activities. The search was performed across multiple academic databases, including Scopus, Web of Science, PubMed, ScienceDirect, and Google Scholar, covering the period from January 2020 to October 2025. The following combinations of keywords and

Boolean operators were used: ("endophytic fungi" OR "endophyte") AND ("*Aspergillus*") AND ("secondary metabolites" OR "natural products") AND ("bioactivity" OR "biological activity" OR "pharmacological activity").

**Inclusion and Exclusion Criteria**

To ensure the scientific relevance and reliability of the data, specific criteria were applied during the literature selection process:

**Inclusion criteria:**

a. Studies reporting the isolation or identification of *Aspergillus* endophytes from plants (particularly medicinal plants).
b. Studies describing the chemical structure or class of secondary metabolites produced by endophytic *Aspergillus*.
c. Publications that include biological activity evaluation (e.g., antimicrobial, cytotoxic, antioxidant, antiviral, or anti-inflammatory assays).
d. Review and research articles indexed in major scientific databases (Scopus, PubMed, or Web of Science).

**Exclusion criteria:**

a. Studies on non-endophytic *Aspergillus* (e.g., pathogenic or saprophytic isolates).
b. Articles lacking information on bioactive compounds or biological activities.
c. Grey literature such as conference abstracts, theses, or non-peer-reviewed reports.

**Data Extraction and Organization**

For each eligible publication, essential information was extracted, including:

a. Fungal species (or strain) and its host plant.
b. Type and class of secondary metabolites identified.
c. Reported biological activities and experimental methods used.
d. Geographical origin and source of isolation.
e. Reference citation (author, year, and DOI).

The data were organized into summary tables to highlight the relationships between *Aspergillus* species, host plants, metabolite classes, and corresponding biological activities. Whenever available, structural details of key compounds were illustrated to emphasize chemical diversity.

**Data Synthesis**

The collected data were analyzed qualitatively through comparative and thematic synthesis. Trends in metabolite diversity, taxonomic distribution, and bioactivity profiles were evaluated to identify research gaps and emerging directions. No meta-analysis or quantitative synthesis was performed due to heterogeneity in bioassay protocols and reporting standards among studies. A PRISMA-style flow diagram was prepared to illustrate the literature selection process, summarizing the total number of articles identified, screened, and included in the final dataset.

## III. RESULTS AND DISCUSSION

**Diversity of Secondary Metabolites in the Genus *Aspergillus***

A comprehensive analysis of published literature reveals that the genus *Aspergillus* stands among the most prolific and chemically versatile producers of bioactive secondary metabolites within endophytic fungi (Zakaria, 2024). Fungal endophytes produce invaluable bioactive metabolic compounds beneficial to humans with antimicrobial, anticancer, antidiabetic, anti-inflammatory, antitumor properties, etc. Some of these bioactive compounds include pestacin,

taxol, camptothecin, ergoflavin, podophyllotoxin, benzopyran, isopestacin, phloroglucinol, tetrahydroxy-1-methylxanthone, salidroside, borneol, dibenzofurane, methyl peniphenone, lipopeptide, peniphenone (Adeleke & Babalola, 2021). This remarkable structural diversity reflects not only the genus's extraordinary biosynthetic potential but also its ecological adaptability to various environmental conditions and host plants. The ability of *Aspergillus* to thrive as an endophyte across diverse plant species from terrestrial herbs to marine-derived (Wang et al., 2025) plants suggests that host microbe interactions play a critical role in modulating its metabolic expression .

At the molecular level, the diversity of *Aspergillus*-derived metabolites is largely attributed to its complex biosynthetic gene clusters (BGCs), which encode enzymes such as polyketide synthases (PKSs), nonribosomal peptide synthetases (NRPSs), and hybrid PKS–NRPS systems. These enzyme complexes are responsible for generating structurally intricate metabolites with diverse biological functions. Recent genome-mining studies have revealed that many of these BGCs remain cryptic or silent under standard laboratory conditions, suggesting that the metabolic capacity of *Aspergillus* is far greater than currently documented. Activation of these silent clusters through co-culture, epigenetic modification, or chemical elicitation represents an emerging strategy to discover novel bioactive compounds (Hagag et al., 2022).

**General Biological Activities of *Aspergillus*-Derived Secondary Metabolites**

Numerous studies have reported that extracts derived from endophytic *Aspergillus* species (Mamangkey et al., 2024), particularly those belonging to *A. flavus, A. niger, and A. fumigatus*, possess remarkable pharmacological potential due to their chemically diverse secondary metabolites. In general, the secondary metabolites synthesized by members of the genus *Aspergillus* including alkaloids, polyketides, terpenoids, and peptides exhibit broad and multispecific biological activities such as antimicrobial, anticancer, antioxidant, anti-inflammatory, antifungal, and antiparasitic effects (Jangid et al., 2024). This extensive spectrum of bioactivities reflects not only the structural complexity of Aspergillus-derived metabolites but also their ability to modulate a wide range of biochemical pathways. Such molecular diversity allows these compounds to engage in specific interactions with various biological targets, including enzymes, cellular membranes, nucleic acids, and intracellular signaling molecules, thereby influencing essential physiological and pathological processes. Consequently, endophytic Aspergillus species represent a promising and underexplored source for the discovery of novel bioactive compounds with potential applications in pharmaceutical, agricultural, and biotechnological fields (Zhu et al., 2023).

Among the most extensively studied species are *Aspergillus fumigatus*, *A. niger*, *A. flavus*, *A. terreus*, and *A. sydowii* (Brandt et al., 2020). Furthermore, comparative chemotaxonomic analyses suggest that metabolite profiles of *Aspergillus* species are influenced by environmental factors such as salinity, temperature, nutrient availability, and host. The identified endophytic fungi included *Aspergillus cavernicola*, *Aspergillus persii*, from *Ziziphus lotus*. GC–MS analysis confirmed the presence of numerous bioactive compounds. All extracts exhibited antibacterial activity against at least two bacterial strains, and most demonstrated antioxidant effects. Among them, the extract from *Aspergillus cavernicola* showed the highest phenolic content, along with superior antioxidant and antibacterial activities, suggesting it as a promising candidate for further pharmacological exploration (Ghazi-Yaker et al., 2024).

In addition to antibacterial effects, several *Aspergillus* metabolites demonstrate potent antifungal and antiparasitic properties. Extracts from *A. terreus* and *A. sydowii*, for example, effectively inhibit the growth of pathogenic fungi such as *Candida albicans*, pathogenic *Aspergillus fumigatus*, and *Cryptococcus neoformans*. Bioactive compounds such as

emericellamide and fellutanine disrupt ergosterol biosynthesis a vital component of fungal cell membranes. Furthermore, antiparasitic activity has been observed against *Plasmodium falciparum* (malaria) and *Leishmania donovani*, primarily through inhibition of key metabolic enzymes and disruption of parasite cell membrane integrity. These findings highlight *Aspergillus* as a promising source of novel antimicrobial and antiparasitic compounds, especially for combating drug-resistant pathogens. *A. fumigatus*, *A. flavus* (Sedjati et al., 2020), and *A. niger*, possess strong inhibitory activity against pathogenic Gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis*, as well as Gram-negative bacteria including *Escherichia coli* and *Pseudomonas aeruginosa*. The antimicrobial mechanisms primarily involve disruption of bacterial membrane integrity, inhibition of protein biosynthesis, and inactivation of essential metabolic enzymes. Compounds such as gliotoxin and terrein are known to penetrate microbial cell walls, causing cytoplasmic leakage and cell death. Moreover, some metabolites act as biofilm inhibitors, which is particularly significant in combating chronic infections caused by antibiotic-resistant bacteria.

Marine-derived *A. sydowii* (Ibrahim et al., 2023), is a prolific source of distinct and structurally varied metabolites such as alkaloids, xanthones, terpenes, anthraquinones, sterols, diphenyl ethers, pyrones, cyclopentenones, and polyketides with a range of bioactivities. *A. sydowii* has capacity to produce various enzymes with marked industrial and biotechnological potential, including α-amylases, lipases, xylanases, cellulases, keratinases, and tannases.

Metabolites such as aspergilol, isoflavonoids, and several phenolic derivatives from *Aspergillus* exhibit potent free radical scavenging activity, neutralizing reactive oxygen species (ROS) and protecting biomolecules from oxidative damage. These compounds reduce lipid peroxidation, enhance the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, and inhibit the production of pro-inflammatory cytokines such as TNF-α and IL-6. Such properties are highly relevant in preventing degenerative diseases including cancer, atherosclerosis, and neurodegenerative disorders. Consequently, *Aspergillus*-derived metabolites hold strong potential for development as nutraceuticals or natural therapeutic agents with protective effects against oxidative stress and chronic inflammation (Vitale et al., 2020).

Secondary metabolites from *Aspergillus* have shown remarkable potential as natural anticancer agents (Alfaifi et al., 2020). A systematic and bibliometric review indicated that several fungal species exhibit strong potential as promising sources of anticancer agents. Conventional chemotherapy drugs such as doxorubicin, actinomycin, and flavonoids serve as standard chemical treatments for various cancers. In contrast, fungi including *Aspergillus niger*, *A. fumigatus*, *A. oryzae*, *A. flavus*, *A. versicolor*, *A. terreus*, *Penicillium citrinum, P. chrysogenum*, and *P. polonicum* have been identified as prolific producers of anticancer metabolites. These fungal-derived compounds have been investigated for their cytotoxic effects against multiple cancer types, including cervical, pancreatic, ovarian, breast, colon, and colorectal cancers, highlighting the potential of these fungi as natural sources for future cancer therapeutics (Noman et al., 2021). Vitexin derived from *Aspergillus flavus* demonstrates significant potential as a lead molecule for developing selective and potent inhibitors that target tumor-suppressor-related proteins in breast cancer. This research establishes an important foundation for the future design of safer and more specific therapeutic agents utilizing bioactive compounds sourced from fungi (Alsharif & Sajer, 2025).

In summary, the genus *Aspergillus* exemplifies a remarkable model for natural product discovery due to its broad biosynthetic repertoire, ecological plasticity, and evolutionary capacity to generate structurally and functionally diverse metabolites. Continued exploration of its endophytic species using integrative approaches combining genomics, metabolomics, and advanced analytical chemistry is essential for uncovering the full spectrum of its bioactive potential.

Overall, secondary metabolites derived from *Aspergillus* exhibit extensive biological potential with significant pharmacological implications. The integration of biotechnological, bioinformatics, and mechanistic approaches is essential to identify specific molecular targets and to optimize the production of these compounds for future therapeutic applications.

## IV. CONCLUSION

This comprehensive review confirms that endophytic fungi of the genus *Aspergillus* are prolific producers of structurally diverse and pharmacologically valuable secondary metabolites. Through a systematic literature search and qualitative synthesis, it was established that *Aspergillus* species such as *A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, and *A. sydowii* play a crucial role in generating bioactive compounds with potent antimicrobial, antioxidant, anticancer, anti-inflammatory, antifungal, and antiparasitic properties.

Additionally, certain *Aspergillus* species, particularly *A. cavernicola* and *A. sydowii*, exhibit exceptional bioactivities that position them as valuable sources for pharmaceutical and nutraceutical development. Metabolites such as gliotoxin, terrein, and vitexin show potential as natural anticancer and antioxidant agents, reinforcing the genus's biomedical significance. In conclusion, *Aspergillus* endophytes represent an underutilized yet promising reservoir of natural bioactive products. Future studies integrating omics technologies, molecular biology, and synthetic biology are essential to fully unlock their therapeutic potential and advance sustainable drug discovery efforts.

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