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Review Article

Endophyte-Derived Natural Products Using *in silico* and *in vitro* Methods for Drug Lead Discovery: A Review

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ABSTRACT

Numerous fungal endophytes produce plant-derived chemicals that are pharmacologically useful, making them well-known sources of naturally occurring, biologically active compounds. Alkaloids, coumarins, flavonoids, glycosides, lignans, phenylpropanoids, quinones, saponins, terpenoids, and xanthones, all produced by endophytic fungi, are common plant-derived therapeutic chemicals included in this study. This overview covers research from the initial discovery of Taxol production by endophytic Taxomyces andreanae in 1993 to mid-2020. The study also discusses the challenges to commercializing this innovative approach in drug development, while emphasizing the significant potential for endophyte-based production of such pharmacologically active chemicals derived from plants. This potential offers an optimistic outlook for future drug development. Thanks to recent advances in the "omics" and "one strain many compounds" (OSMAC) methodologies, fungal endophytes have become powerful alternatives to traditional methods.

Keywords: Alkaloids, Drug Development, Flavonoids, Glycosides, Lignans, Phenylpropanoids, Quinones, Saponins, Secondary Metabolites, Terpenoids, Xanthones, Taxol.

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INTRODUCTION

Microorganisms known as endophytes, including bacteria and fungi, live inside healthy plant tissues without causing harm.[1-3] With plants, they establish symbiotic relationships in which the endophyte and the plant gain from one another. Endophytes frequently aid plants in fending off pests and diseases, surviving environmental stress, and even improving their growth. The endophytes receive nutrients and a secure environment from the plants in exchange.[4-6] The capacity of endophytes to create secondary metabolites, special chemical substances that are not directly engaged in growth or reproduction but play roles in defense and survival, is what scientists and pharmaceutical researchers find particularly intriguing.[7-11] Many of these substances are bioactive, meaning they can interact with biological systems to produce beneficial effects, such as reducing inflammation, killing germs, or stopping the growth of cancer cells.[12-16] It's interesting to note that some of these metabolites are quite close to those produced by the host plant, or even identical. For instance, it was established that the Pacific yew tree's endophytic fungus, *Taxomyces andreanae*, produces the well-known anticancer medication Taxol, which was previously believed to originate only from the plant.[17-20] Finding beneficial compounds in endophytes has historically involved a time-consuming procedure. Using surface sterilization, scientists first separate endophytes from plant tissues and cultivate them on a nutritional medium.[21-25] After that, they grow these microbes in different environments and use solvents to extract the metabolites they generate. To determine if these crude extracts contain antibacterial, antifungal, anticancer, or other desirable properties, bioassays are used.[26-30] In order to identify and comprehend the active chemical, additional procedures such as purification and structural analysis (using techniques like NMR and mass spectrometry) are conducted if a promising activity is discovered.[31-35] Despite its effectiveness, this procedure is costly, time-consuming, and fraught with difficulties. Numerous endophytes are challenging to cultivate in the lab, and some cannot generate beneficial chemicals unless they are subjected to particular stressors or environmental conditions. Furthermore, the discovery process may be slowed down by the sheer volume of extracts that must be screened.[36-40] To overcome these obstacles, researchers are now using *in silico* (computer-based) techniques to streamline drug discovery. These techniques, even before they undergo laboratory testing, can accurately predict, screen, and rank potential medication candidates.[41-45] One such method is molecular docking, where scientists model how a molecule may fit into and interact with a disease-related target protein using Three-Dimensional (3D) models. This predictive power aids in identifying the most promising chemicals.[46-50]

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ADMET prediction, which stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity, is an additional method used to assess whether a compound is likely to be safe and effective in humans. Recently, researchers have also been increasingly utilizing Artificial Intelligence (AI) and machine learning models trained on large datasets of known medicinal molecules.[51-55] These models can predict biological activity, filter out less promising substances, and even suggest structural modifications to enhance safety or efficacy. By integrating these *in silico* technologies with traditional *in vitro* techniques, scientists can save time and money.[56-60]

Role of Endophytes in Drug Discovery

Endophytes, the microorganisms that live inside plants, are a rich source of bioactive chemicals with potential applications in drug development (Figure 1). These organisms produce many secondary metabolites with antibacterial, anticancer, anti-inflammatory, and other medicinal properties. Studying these endophytes not only offers a promising way to discover new medicines but also gives hope in the fight against drug resistance.[61-66]

A Treasure-trove of Bioactive Compounds

Alkaloids, flavonoids, terpenoids, polyketides, and peptides are among the many natural products that endophytes can produce, as shown in Figure 2. These compounds have biological activities such as antibacterial (killing or inhibiting bacteria), antifungal (fighting fungal infections), antiviral (blocking viruses), and anticancer (inhibiting or killing cancer cells).[67-71]

Alternative and Sustainable Sources of Plant-Based Drugs

Endophytes offer a sustainable alternative to large-scale production of plant-derived drugs. Many medicinal plants are slow-growing, rare, or endangered, but the ability to cultivate endophytes in labs provides a new source of important compounds. This promising avenue of research offers hope for the future of medicinal research, especially for drugs that are expensive or difficult to synthesize chemically, as shown in Figure 3.[72-77]

Chemical Diversity and Novelty

Endophytes frequently inhabit distinct ecological niches and generate substances that are not found elsewhere. A few of these are completely novel chemical structures that have never been documented before. Because of this, endophytes are a promising source of "first-in-class" drug candidates, which are entirely novel treatments for illnesses for which there is currently no cure.[78-82]

Symbiotic Evolution and Metabolic Potential

Over millions of years, endophytes have co-evolved with their host plants, which is thought to have an impact on the types of metabolites they produce.[83,84] Some scientists even believe that endophytes "learn" to mimic the chemistry of their host plants, leading to similar or complementary pharmacological effects (Figure 4). This evolutionary relationship gives endophytes an additional layer of value in drug discovery.[83-85]

Potential in Drug Lead Optimization

Endophytes are also crucial in the early phases of drug development, which are sometimes referred to as "lead discovery." Scientists can identify lead compounds with promising activity that can be chemically altered to enhance their drug-like qualities (such as solubility, stability, and selectivity) by isolating and testing endophytic metabolites.[86-91]

Use in Combination Therapies

For instance, compounds that improve the action of antibiotics or decrease resistance in cancer cells may be derived from endophytes and used as adjuvants in combination therapy. Other compounds derived from endophytes may also work well in combination with existing medications, increasing the effectiveness of treatments or lowering the dosage needed.[92-94]

Industrial and Pharmaceutical Applications

With the aid of genetic engineering and fermentation technologies, it is now feasible to scale up the production of specific metabolites from endophytes. Several pharmaceutical companies and research institutions are investigating endophytes for their potential to produce commercial drugs, food preservatives, cosmetic ingredients, and agricultural biopesticides.[94-96]

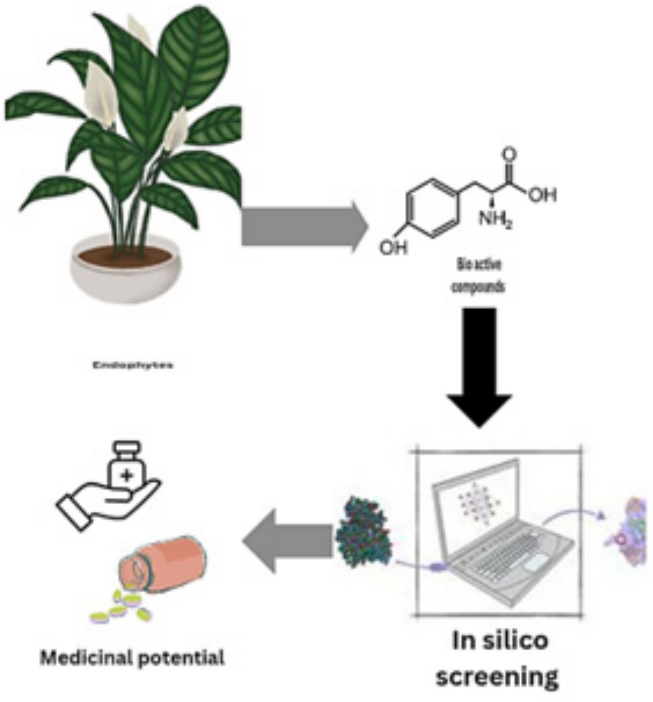

Figure 1: Role of entophytes in producing bioactive compounds.

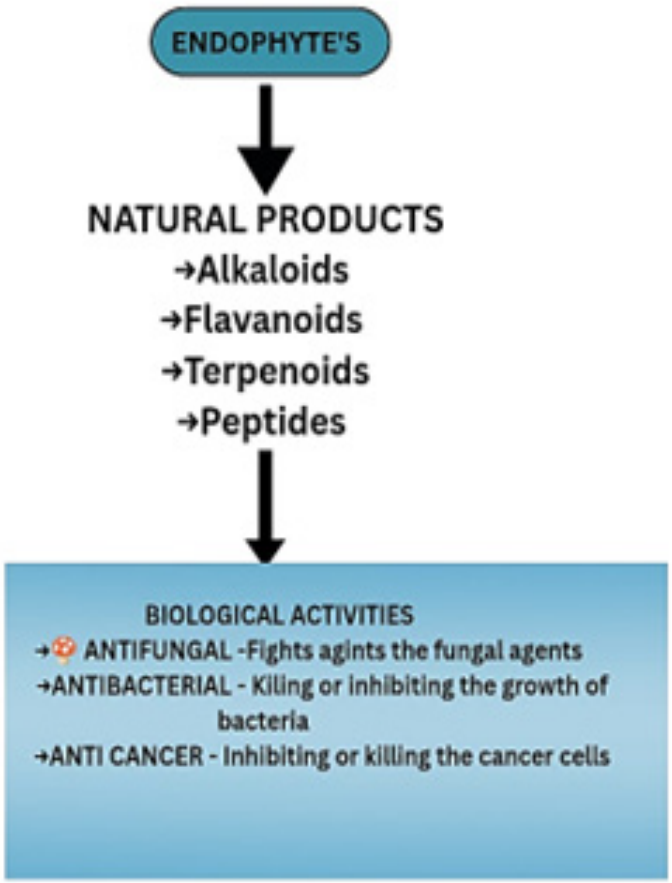

Figure 2: Role of entophytes in producing secondary metabolites for treating different diseases.

In silico Approaches in Endophyte Research

With computational tools to anticipate and study the behavior of these helpful microbes and their interactions with host plants, *in silico* techniques are becoming increasingly valuable in endophyte research. These techniques speed up the identification of new bioactive compounds, clarify dophyte-host interactions, and potentially maximize their uses in medicine and agriculture.[97-99]

Genome mining

Genome mining is a computational approach that analyzes an organism's genetic information (genomes) to discover new natural products, such as potential medicines. It emphasizes identifying and describing the Biosynthetic Gene Clusters (BGCs) that produce these natural compounds within genomes (Figure 5).

Tools

➢antiSMASH [antibiotics and Secondary Metabolite Analysis Shell].

➢PRISM [Prediction Informatics for Secondary Metabolism].

➢BAGEL.[100-104]

Molecular Docking and Virtual Screening

Molecular docking

Molecular docking is a computational method that predicts the binding pose and affinity of a small molecule (ligand) to a protein target.

Purpose

Molecular docking is a computational method that predicts the binding pose and affinity of a small molecule (ligand) to a protein target.

Applications

Structure-based drug design

Docking is a core component of structure-based drug design, where the 3D structure of a protein target is known.[105-109]

Virtual screening

Docking is used to screen large libraries of molecules against the target protein to identify potential drug candidates.

Understanding protein-ligand interactions

Docking helps researchers understand the nature of interactions between a drug and its target protein, which can be useful for optimizing drug properties.[110-113]

Virtual Screening

Virtual Screening (VS) is a computational method that uses computational techniques to sift through large collections of chemical compounds to identify those that are likely to bind to a specific protein target (Figure 6).

Purpose

VS aims to identify promising drug candidates from a vast library of compounds, reducing the number of compounds that need to be tested experimentally.

Applications

- Drug discovery: VS is a crucial step in modern drug discovery, helping to identify potential drug candidates for various diseases.
- Lead optimization: VS canals can be used to optimize the properties of existing drug leads.
- Identifying new drug targets: VS can help identify new proteins that could be targeted by drugs.[114-117]

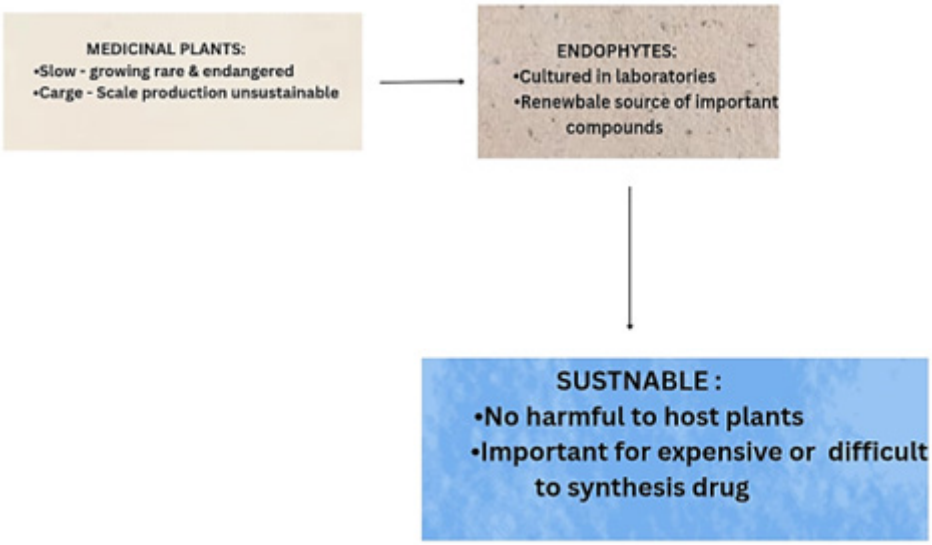

Figure 3: Alternative and Sustainable Sources of Plant-Based Drugs.

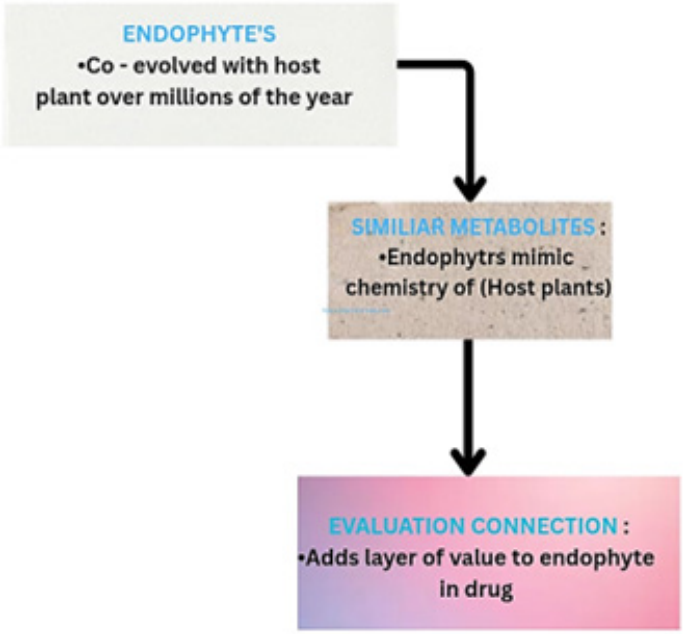

Figure 4: Symbiotic Evolution and Metabolic Potential.

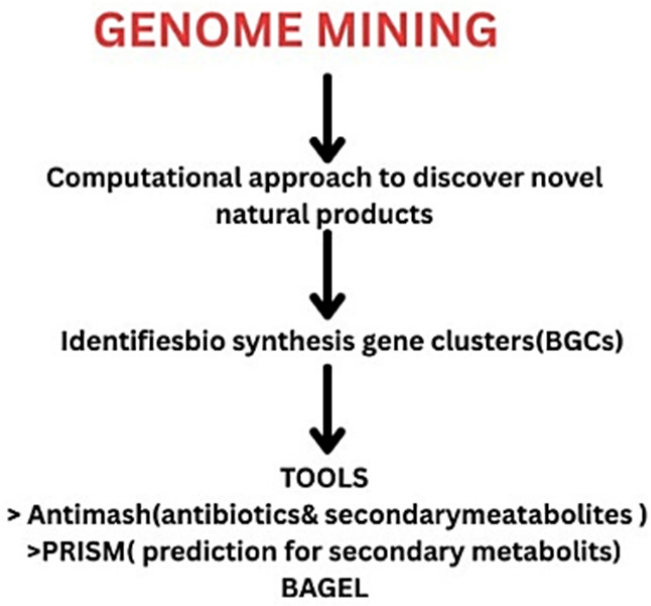

Figure 5: Genome Mining.

In vitro Methods for Identifying Drug Lead Bioactivity

Mechanisms and pharmacological potential are confirmed by *in vitro* experiments, which validate *in silico* predictions. Important techniques include:

HTS, or high-throughput screening

HTS quickly filters either refined chemicals or crude extracts. For instance, in HCT-15, chloroformic extracts of *Chaetomium globosum* decreased cell viability to 9.26%-16.3% in La cell lines for cancer. A 19.93 mm zone of inhibition was observed in extracts from *Albophoma* sp. BAPR5 against Staphylococcus epidermidis. Methods: Ames's test, disc diffusion (antimicrobial), and MTT assay (cytotoxicity).[118-120]

Fractionation Guided by Bioactivity

This technique uses chromatography (e.g., HPLC) to separate active chemicals from complicated mixtures. For instance, Polyhydroxy anthraquinones from *Penicillium restrictum* were isolated and tested for quorum-sensing inhibition against MRSA.[121,122]

Enzyme Inhibition Assays

These assays evaluate compounds against specific enzymes. For example, Tripalmitin from *Zasmidium* sp. inhibited α-glucosidase,

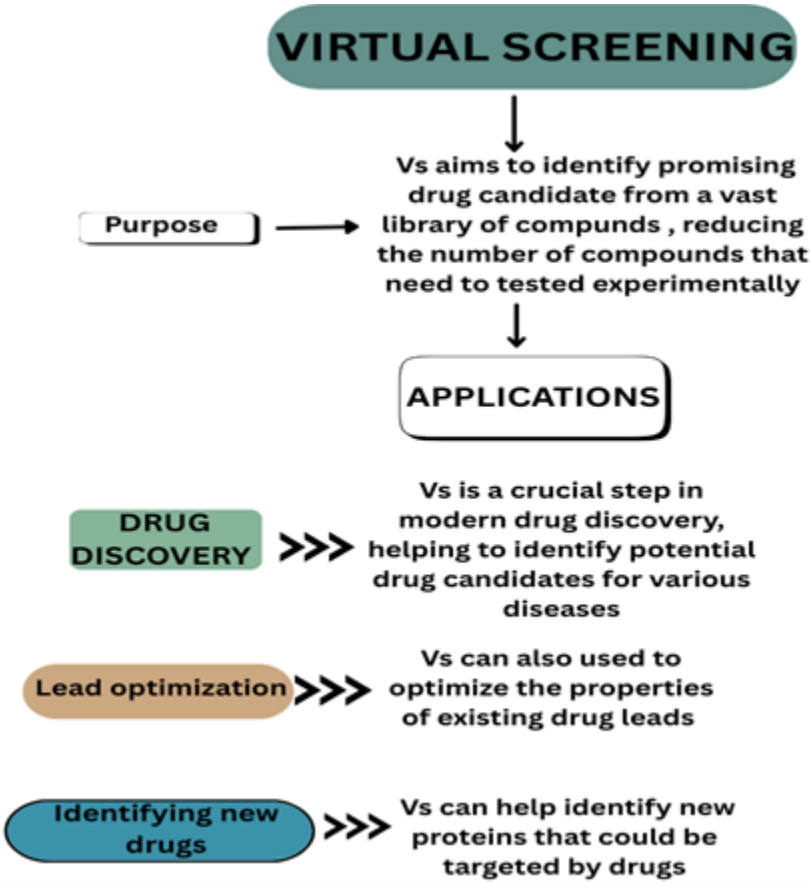

Figure 6: Virtual Screening.

supporting its use in antidiabetic treatments. Cowpea-derived peptides (IAF, QGF, QDF) inhibited HMG-CoA reductase by 69%-78%, validating their cholesterol-lowering effects.[123-125]

Antimicrobial and Anticancer Assays

Compounds are tested against pathogens or cancer cells. For example, *Taxomyces andreanae* Taxol exhibited potent cytotoxicity against breast cancer cells. *Albophoma* sp. BAPR5 extracts showed antifungal and antibacterial activity.[126-128]

Antioxidant and Anti-inflammatory Assay

Antioxidant activity is assessed using DPPH or ABTS assays, while anti-inflammatory effects are tested via cytokine suppression. For example, *Chaetomium globosum* extracts showed IC_{50} values of 45.16-50.55 µg/mL.[129,130]

CONCLUSION

In conclusion, fungal endophytes are a highly promising and underexplored source of natural bioactive compounds with great potential for drug lead discovery. The discovery of key plant-derived compounds, such as paclitaxel, produced by endophytic fungi, has opened new pathways for sustainable and alternative production methods. Despite challenges like unculturable strains, loss of metabolite biosynthetic capacity during preservation, and reliance on host plant diversity, advances in co-cultivation, genomics, and chemical elicitation techniques are increasing the yield and diversity of pharmacologically important metabolites. Ongoing exploration and technological innovations will promote the development of endophyte-based drug candidates, establishing fungal endophytes as a valuable resource in the pharmaceutical industry for novel therapeutic agents.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Hardoim PR, van Overbeek LS, Berg G, Pirttilä AM, Compant S, Campisano A, *et al.* The hidden world within plants: Ecological and evolutionary considerations for defining functioning of microbial endophytes. *Microbiol Mol Biol Rev*. 2015; 79(3): 293-320.
2. Ryan RP, Germaine K, Franks A, Ryan DJ, Dowling DN. Bacterial endophytes: Recent developments and applications. *FEMS Microbiol Lett*. 2008; 278(1): 1-9.
3. Rodriguez RJ, White JF, Arnold AE, Redman RS. Fungal endophytes: Diversity and functional roles. *New Phytol*. 2009; 182(2): 314-30.
4. Omomowo IO, Babalola OO. Bacterial and fungal endophytes: Tiny giants with immense beneficial potential for plant growth and sustainable agricultural productivity. *Microorganisms*. 2019; 7(11): 481.
5. White JF, Kingsley KL, Zhang Q, Verma R, Obi N, Dvinskikh S, *et al.* Review: Endophytic microbes and their potential applications in crop management. *Pest Manag Sci*. 2019; 75(10): 2558-65.
6. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: A treasure house of bioactive compounds of medicinal importance. *Front Microbiol*. 2016; 7: 1538.
7. Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. *J Nat Prod*. 2004; 67(2): 257-68.
8. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: A treasure house of bioactive compounds of medicinal importance. *Front Microbiol*. 2016; 7: 1538.
9. Kusari S, Hertweck C, Spiteller M. Chemical ecology of endophytic fungi: Origins of secondary metabolites. *Chem Biol*. 2012; 19(7): 792-8.
10. Pimentel MR, Molina G, Dionísio AP, Maróstica MR, Pastore GM. The use of endophytes to obtain bioactive compounds and their application in biotransformation process. *Biotechnol Res Int*. 2011; 2011: 576286.
11. Venieraki A, Dimou M, Pergalis P, Kefalogianni I, Chorianopoulou SN, Katinakis P. The genetic diversity of culturable nitrogen-fixing bacteria in the rhizosphere of wheat. *Microb Ecol*. 2011; 61(2): 277-85
12. Zhao J, Shan T, Mou Y, Zhou L. Plant-derived bioactive compounds produced by endophytic fungi. *Mini Rev Med Chem*. 2010; 10(9): 963-78.
13. Strobel G, Daisy B. Bioprospecting for microbial endophytes and their natural products. *Microbiol Mol Biol Rev*. 2003; 67(4): 491-502.
14. Kusari S, Pandey SP, Spiteller M. Untapped mutualistic paradigms linking host plant and endophytic fungal chemistry. *Front Microbiol*. 2013; 4: 16.
15. Aly AH, Debbab A, Proksch P. Fungal endophytes: Unique plant inhabitants with great promises. *Appl Microbiol Biotechnol*. 2011; 90(6): 1829-45.
16. Gunatilaka AAL. Natural products from plant-associated microorganisms: Distribution, structural diversity, bioactivity, and implications of their occurrence. *J Nat Prod*. 2006; 69(3): 509-26
17. Stierle A, Strobel G, Stierle D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. *Science*. 1993; 260(5105): 214-6.
18. Kusari S, Zühlke S, Spiteller M. An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. *J Nat Prod*. 2009; 72(1): 2-7.
19. Venugopalan A, Srivastava S. Endophytes as *in vitro* production platforms of high-value plant secondary metabolites. *Biotechnol Adv*. 2015; 33(6 Pt 1):873-87.
20. Staniek A, Woerdenbag HJ, Kayser O. Endophytes as a source of natural products: Diversity, emergence, and bioactivity. *Fitoterapia*. 2008; 79(7-8): 491-9.
21. Schulz B, Wanke U, Draeger S, Aust HJ. Endophytes from herbaceous plants and shrubs: Effectiveness of surface sterilization methods. *Mycol Res*. 1993; 97(12): 1447-50.
22. Strobel GA, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. *J Nat Prod*. 2004; 67(2): 257-68.
23. Petrini O. Fungal endophytes of tree leaves. In: Andrews JH, Hirano SS, editors. *Microbial ecology of leaves*. New York: Springer; 1991. p. 179-97.
24. Arnold AE, Maynard Z, Gilbert GS, Coley PD, Kursar TA. Are tropical fungal endophytes hyperdiverse? *Ecol Lett*. 2000; 3(4): 267-74.
25. Hallmann J, Quadt-Hallmann A, Mahaffee WF, Kloepper JW. Bacterial endophytes in agricultural crops. *Can J Microbiol*. 1997; 43(10): 895-914.
26. Wink M. Modes of action of herbal medicines and plant secondary metabolites. *Medicines* (Basel). 2015; 2(3): 251-86.
27. Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. *J Nat Prod*. 2004; 67(2): 257-68.
28. Schulz B, Boyle C. The endophytic continuum. *Mycol Res*. 2005; 109(6): 661-86.
29. Aly AH, Debbab A, Proksch P. Fungal endophytes: Unique plant inhabitants with great promises. *Appl Microbiol Biotechnol*. 2011; 90(6): 1829-45.
30. Li JY, Strobel G, Sidhu RS, Hess WM, Ford EJ. Endophytic taxol-producing fungi from bald cypress, *Taxodium distichum*. *Microbiology*. 1996; 142(8): 2223-6.
31. Wolfender JL, Queiroz EF, Hostettmann K. Phytochemistry in the postgenomic era: New strategies for natural product discovery. *Phytochem Rev*. 2006; 5(2-3): 409-26.
32. Li JY, Strobel GA, Sidhu RS, Hess WM, Ford EJ. Endophytic taxol-producing fungi from bald cypress, *Taxodium distichum*. *Microbiology*. 1996; 142(8): 2223-6.
33. Aly AH, Debbab A, Proksch P. Fifty years of drug discovery from fungi. *Fungal Divers*. 2011; 50: 3-19.
34. Schueffler A, Anke T. Fungal natural products in research and development. *Nat Prod Rep*. 2014; 31(10): 1425-48.
35. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: A treasure house of bioactive compounds of medicinal importance. *Front Microbiol*. 2016; 7: 1538.
36. Zhang HW, Song YC, Tan RX. Biology and chemistry of endophytes. *Nat Prod Rep*. 2006; 23(5): 753-71.
37. Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. *J Nat Prod*. 2004; 67(2): 257-68.
38. Pimentel MR, Molina G, Dionísio AP, Maróstica MR, Pastore GM. The use of endophytes to obtain bioactive compounds and their application in biotransformation processes. *Biotechnol Res Int*. 2011; 2011: 576286.
39. Staniek A, Woerdenbag HJ, Kayser O. Endophytes as a source of natural products: Diversity, emergence, and bioactivity. *Fitoterapia*. 2008; 79(7-8): 491-9.
40. Li HY, Wei DQ, Shen M, Zhou ZP. Endophytes and their role in phytoremediation. *Fungal Divers*. 2012; 54: 11-18.
41. Ekins S, Mestres J, Testa B. *In silico* pharmacology for drug discovery: Methods for virtual ligand screening and profiling. *Br J Pharmacol*. 2007; 152(1): 9-20.
42. Sliwoski G, Kothiwale S, Meiler J, Lowe EW Jr. Computational methods in drug discovery. *Pharmacol Rev*. 2014; 66(1): 334-95.
43. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. *Curr Top Med Chem*. 2014; 14(16): 1923-38.
44. Chen Y, Kirchmair J. Cheminformatics in natural product-based drug discovery. *Mol Inform*. 2020; 39(9): e2000171.
45. López-Vallejo F, Giulianotti MA, Houghten RA, Medina-Franco JL. Expanding the medicinally relevant chemical space with compound libraries. *Drug Discov Today*. 2012; 17(13-14): 718-26.
46. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: Methods and applications. *Nat Rev Drug Discov*. 2004; 3(11): 935-49.
47. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: A powerful approach for structure-based drug discovery. *Curr Comput Aided Drug Des*. 2011; 7(2): 146-57.
48. Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. *Molecules*. 2015; 20(7): 13384-421.
49. Yuriev E, Ramsland PA. Latest developments in molecular docking: 2010-2011 in review. *J Mol Recognit*. 2013; 26(5): 215-39.
50. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. *Curr Top Med Chem*. 2014; 14(16): 1923-38.
51. Van de Waterbeemd H, Gifford E. ADMET *in silico* modelling: Towards prediction paradise? *Nat Rev Drug Discov*. 2003; 2(3): 192-204.
52. Cheng F, Li W, Zhou Y, Shen J, Wu Z, Liu G, *et al.* admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *J Chem Inf Model*. 2012; 52(11): 3099-105.
53. Dong J, Wang NN, Yao ZJ, Zhang L, Cheng Y, Ouyang D, *et al.* ADMETlab: A platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. *J Cheminform*. 2018; 10(1): 29.
54. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, *et al.* Applications of machine learning in drug discovery and development. *Nat Rev Drug Discov*. 2019; 18(6): 463-77.
55. Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. *Drug Discov Today*. 2018; 23(6): 1241-50.
56. Sliwoski G, Kothiwale S, Meiler J, Lowe EW Jr. Computational methods in drug discovery. *Pharmacol Rev*. 2014; 66(1): 334-95.
57. Ekins S, Mestres J, Testa B. *In silico* pharmacology for drug discovery: Methods for virtual ligand screening and profiling. *Br J Pharmacol*. 2007; 152(1): 9-20.
58. Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. *Drug Discov Today*. 2018; 23(6): 1241-50.
59. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, *et al.* Applications of machine learning in drug discovery and development. *Nat Rev Drug Discov*. 2019; 18(6): 463-77.
60. Schneider G. Automating drug discovery. *Nat Rev Drug Discov*. 2018; 17(2): 97-113.
61. Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. *J Nat Prod*. 2004; 67(2): 257-68.
62. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: A treasure house of bioactive compounds of medicinal importance. *Front Microbiol*. 2016; 7: 1538.
63. Aly AH, Debbab A, Proksch P. Fungal endophytes: Unique plant inhabitants with great promises. *Appl Microbiol Biotechnol*. 2011; 90(6): 1829-45.
64. Kusari S, Hertweck C, Spiteller M. Chemical ecology of endophytic fungi: Origins of secondary metabolites. *Chem Biol*. 2012; 19(7): 792-8.
65. Gupta S, Chaturvedi P, Kulkarni MG, Van Staden J. A critical review on exploiting the pharmaceutical potential of plant endophytic fungi. *Biotechnol Adv*. 2020; 39: 107462.
66. Deshmukh SK, Verekar SA, Bhave SV. Endophytic fungi: A reservoir of antibacterials. *Front Microbiol*. 2014; 5: 715.
67. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. *J Nat Prod*. 2007; 70(3): 461-77.
68. Venugopalan A, Srivastava S. Endophytes as *in vitro* production platforms of high value plant secondary metabolites. *Biotechnol Adv*. 2015; 33(6 Pt 1):873-87.

69. Chutulo EC, Chalannavar RK. Endophytic mycoflora and their bioactive compounds from *Azadirachta indica*: A comprehensive review. *J Fungi*. 2018; 4(2): 42.
70. Huang WY, Cai YZ, Hyde KD, Corke H, Sun M. Endophytic fungi from medicinal plants: A potential source of bioactive secondary metabolites. *Fitoterapia*. 2008; 79(9): 586-9.
71. Kusari S, Singh S, Jayabaskaran C. Biotechnological potential of plant-associated endophytic fungi: Hope versus hype. *Trends Biotechnol*. 2014; 32(6): 297-303.
72. Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms. *J Nat Prod*. 2004; 67(2): 257-68.
73. Kusari S, Lamshöft M, Spiteller M. Aspergillus fumigatus Fresenius, an endophytic fungus from *Juniperus communis* L. Horstmann as a novel source of the anticancer pro-drug deoxypodophyllotoxin. *J Appl Microbiol*. 2009; 107(3): 1019-30.
74. Venugopalan A, Srivastava S. Endophytes as *in vitro* production platforms of high value plant secondary metabolites. *Biotechnol Adv*. 2015; 33(6 Pt 1):873-87.
75. Kusari S, Singh S, Jayabaskaran C. Biotechnological potential of plant-associated endophytic fungi: Hope versus hype. *Trends Biotechnol*. 2014; 32(6): 297-303.
76. Zhang HW, Song YC, Tan RX. Biology and chemistry of endophytes. *Nat Prod Rep*. 2006; 23(5): 753-71.
77. Deshmukh SK, Verekar SA, Bhave SV. Endophytic fungi: A reservoir of antibacterials. *Front Microbiol*. 2014; 5: 715.
78. Strobel G, Daisy B. Bioprospecting for microbial endophytes and their natural products. *Microbiol Mol Biol Rev*. 2003; 67(4): 491-502.
79. Aly AH, Debbab A, Proksch P. Fifty years of drug discovery from fungi. *Fungal Divers*. 2011; 50: 3-19.
80. Kusari S, Hertweck C, Spiteller M. Chemical ecology of endophytic fungi: Origins of secondary metabolites. *Chem Biol*. 2012; 19(7): 792-8.
81. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 40 years. *J Nat Prod*. 2012; 75(3): 311-35.
82. Kaul S, Gupta S, Ahmed M, Dhar MK. Endophytic fungi from medicinal plants: A treasure hunt for bioactive metabolites. *Phytochem Rev*. 2012; 11(4): 487-505.
83. Rodriguez RJ, White JF Jr, Arnold AE, Redman RS. Fungal endophytes: Diversity and functional roles. *New Phytol*. 2009; 182(2): 314-30.
84. Kaul S, Ahmed M, Zargar K, Sharma P, Dhar MK. Prospecting endophytic fungal assemblages of *Digitalis lanata* Ehrh. (foxglove) as a novel source of digoxin: A cardiac glycoside. *3 Biotech*. 2013; 3(4): 335-40.
85. Kusari S, Zühlke S, Spiteller M. An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. *J Nat Prod*. 2009; 72(1): 2-7.
86. Stierle A, Strobel G, Stierle D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. *Science*. 1993; 260(5105): 214-6.
87. Zhang HW, Song YC, Tan RX. Biology and chemistry of endophytes. *Nat Prod Rep*. 2006; 23(5): 753-71.
88. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: A treasure house of bioactive compounds of medicinal importance. *Front Microbiol*. 2016; 7: 1538.
89. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 40 years. *J Nat Prod*. 2012; 75(3): 311-35.
90. Gouda S, Das G, Sen SK, Shin HS, Patra JK. Endophytes: A treasure house of bioactive compounds of medicinal importance. *Front Microbiol*. 2016; 7: 1538.
91. Gupta S, Chaturvedi P, Kulkarni MG, Van Staden J. A critical review on exploiting the pharmaceutical potential of plant endophytic fungi. *Biotechnol Adv*. 2020; 39: 107462.
92. Singh M, Kumar A, Singh R, Pandey KD. Endophytic bacteria: A new source of bioactive compounds. *3 Biotech*. 2017; 7(5): 315.
93. Deshmukh SK, Verekar SA, Bhave SV. Endophytic fungi: A reservoir of antibacterials. *Front Microbiol*. 2014; 5: 715.
94. Tan RX, Zou WX. Endophytes: A rich source of functional metabolites. *Nat Prod Rep*. 2001; 18(4): 448-59.
95. Kusari S, Singh S, Jayabaskaran C. Biotechnological potential of plant-associated endophytic fungi: Hope versus hype. *Trends Biotechnol*. 2014; 32(6): 297-303.
96. Zhang HW, Song YC, Tan RX. Biology and chemistry of endophytes. *Nat Prod Rep*. 2006; 23(5): 753-71.
97. Mishra P, Kumar A, Panda D, Mohanty S. *In silico* approaches for exploring endophytes as a source of novel bioactive metabolites. *Comput Biol Chem*. 2021; 90: 107372.
98. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. *Nat Rev Drug Discov*. 2015; 14(2): 111-29.
99. Skellam E. Strategies for engineering natural product biosynthesis in fungi. *Trends Biotechnol*. 2019; 37(4): 416-27.
100. Blin K, Shaw S, Steinke K, Villebro R, Ziemert N, Lee SY, *et al.* antiSMASH 5.0: Updates to the secondary metabolite genome mining pipeline. *Nucleic Acids Res*. 2019; 47(W1):W81-7.
101. Skinnider MA, Merwin NJ, Johnston CW, Magarvey NA. PRISM 3: Expanded prediction of natural product chemical structures from microbial genomes. *Nucleic Acids Res*. 2017; 45(W1):W49-54.
102. van Heel AJ, de Jong A, Song C, Viel JH, Kok J, Kuipers OP. BAGEL4: A user-friendly web server to thoroughly mine RiPPs and bacteriocins. *Nucleic Acids Res*. 2018; 46(W1):W278-81.
103. Cimermancic P, Medema MH, Claesen J, Kurita K, Brown LCW, Mavrommatis K, *et al.* Insights into secondary metabolism from a global analysis of prokaryotic biosynthetic gene clusters. *Cell*. 2014; 158(2): 412-21.
104. Medema MH, Fischbach MA. Computational approaches to natural product discovery. *Nat Chem Biol*. 2015; 11(9): 639-48.
105. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: Methods and applications. *Nat Rev Drug Discov*. 2004; 3(11): 935-49.
106. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: A powerful approach for structure-based drug discovery. *Curr Comput Aided Drug Des*. 2011; 7(2): 146-57.
107. Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. *Molecules*. 2015; 20(7): 13384-421.
108. Yuriev E, Ramsland PA. Latest developments in molecular docking: 2010-2011 in review. *J Mol Recognit*. 2013; 26(5): 215-39.
109. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. *Curr Top Med Chem*. 2014; 14(16): 1923-38.
110. Shoichet BK, McGovern SL, Wei B, Irwin JJ. Lead discovery using molecular docking. *Curr Opin Chem Biol*. 2002; 6(4): 439-46.
111. Yuriev E, Holien J, Ramsland PA. Improvements, trends, and new ideas in molecular docking: 2012-2013 in review. *J Mol Recognit*. 2015; 28(10): 581-604.
112. Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. *Molecules*. 2015; 20(7): 13384-421.
113. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. *Curr Top Med Chem*. 2014; 14(16): 1923-38.
114. Shoichet BK. Virtual screening of chemical libraries. *Nature*. 2004; 432(7019): 862-5.
115. Walters WP, Stahl MT, Murcko MA. Virtual screening—an overview. *Drug Discov Today*. 1998; 3(4): 160-78.
116. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. *Curr Top Med Chem*. 2014; 14(16): 1923-38.
117. Lavecchia A, Di Giovanni C. Virtual screening strategies in drug discovery: A critical review. *Curr Med Chem*. 2013; 20(23): 2839-60.
118. Macarron R, Banks MN, Bojanic D, Burns DJ, Cirovic DA, Garyantes T, *et al.* Impact of high-throughput screening in biomedical research. *Nat Rev Drug Discov*. 2011; 10(3): 188-95.
119. Shoemaker RH. The NCI60 human tumour cell line anticancer drug screen. *Nat Rev Cancer*. 2006; 6(10): 813-23.
120. Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J Immunol Methods*. 1983; 65(1-2): 55-63.
121. Bugni TS, Ireland CM. Marine-derived fungi: a chemically and biologically diverse group of microorganisms. *Nat Prod Rep*. 2004; 21(1): 143-63.
122. Choma IM, Grzelak EM. Bioautography detection in thin-layer chromatography. *J Chromatogr A*. 2011; 1218(19): 2684-91.
123. Sales PM, Souza PM, Simeoni LA, Silveira D. α-Amylase inhibitors: a review of raw material and isolated compounds from plant source. *J Pharm Pharm Sci*. 2012; 15(1): 141-83.
124. Sarmadi BH, Ismail A. Antioxidative peptides from food proteins: a review. *Peptides*. 2010; 31(10): 1949-56.
125. Funke I, Melzig MF. Traditionally used plants in diabetes therapy - phytotherapeutics as inhibitors of α-amylase activity. *Rev Bras Farmacogn*. 2006; 16(1): 1-5.
126. Stierle A, Strobel G, Stierle D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. *Science*. 1993; 260(5105): 214-6.
127. Strobel G, Daisy B. Bioprospecting for microbial endophytes and their natural products. *Microbiol Mol Biol Rev*. 2003; 67(4): 491-502.
128. Kusari S, Hertweck C, Spiteller M. Chemical ecology of endophytic fungi: origins of secondary metabolites. *Chem Biol*. 2012; 19(7): 792-8.
129. Singh BN, Singh BR, Singh RL, Prakash D, Dhakarey R, Upadhyay G, *et al.* Polyphenolics from various extracts/fractions of red onion (*Allium cepa*) peel with potent antioxidant and antibacterial activities. *Food Chem Toxicol*. 2009; 47(6): 1161-7.
130. Vaz ABM, Mota RC, Bomfim MRQ, Vieira MLA, Zani CL, Rosa CA, *et al.* Antimicrobial activity and induction of defense responses in plants by endophytic fungi. *PLoS One*. 2009; 4(3): e4284.

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