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REVIEW

Bioprospecting of Lapachol Producing Endophytic Fungi

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Abstract

Background: **The association of endophytic fungi with medicinal plants has been one of the evolving areas of research in the past few decades. The secondary metabolites produced owing to such associations have been recognised for a wide range of biological activities.**

Objectives: **The aim of the present review is to highlight the isolation of lapachol from endophytic microorganisms with an emphasis on its biotransformation to improve its efficacy.**

Methodology: **The researchers followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Published scientific articles on endophytes, host−pathogen interaction and lapachol isolation were collected from reputed journals from 1960 to 2022 using electronic databases using the key words as stated. Following that, the authors chose the required papers based on the criteria they devised. The data was extracted using the common research elements found in the publications.**

Results and discussion: **Lapachol is one such secondary metabolite known for potent antitumor properties. Synthesis of lapachol and its isolation from plant sources have been reported but an expensive process. Therefore, bioprospecting of this metabolite from endophytic fungi have been evaluated by a few researchers. It has been identified that *A. niger* and *Alternaria alternata* along with some of the filamentous endophytic fungi have been identified to produce lapachol. Some findings of biotransformation of lapachol to render it more potent have also been reported in the present review.**

Conclusion: **Lapachol is one of the plant secondary metabolites that possess several therapeutic benefits. Owing to its isolation being highly expensive from plant sources, endophytes have been exploited. Furthering to the isolation, the biotrasformation of this bioactive molecule to enhance its efficiency has proven to be useful. In this regard, this review has enlightened some of the biotransformed lapachol and its derivatives with special emphasis on the endophytes that produce them. This review comprehensively highlights the various endophytic sources for lapachol production and its biotransformed derivatives.**

Keywords: Endophytic, Secondary metabolites, Lapachol, Bioprospecting, *Alternaria alternata*

1. Introduction

Bioactive compounds have been increasingly popular in pharmaceuticals and naturopathy industry in recent years as a result of their human and plant health advantages. Although such compounds from plant sources have been popular, microbial productions are gaining popularity for various benefits [1]. Microorganisms alone or in collaboration with their plant hosts are known to produce enumerable bioactives with noteworthy therapeutic abilities. Endophytes, or microbes that live inside plant tissues, create a variety of these chemicals as well [2]. Endophytes have synthesized a number of new antibiotics that are effective against multidrug-resistant bacteria and are under

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various levels of clinical trials. Several other therapeutic properties are also identified by such metabolites produced from endophytic origin. In addition, endophytic inoculation to plants promotes plant growth while also modulating the production of bioactive molecules with high medicinal potential [3]. This review will not exhaustively present the list of plant-associated microorganisms or the compounds produced by them, as these topics have already been covered. We also won't go over the precise methods for extracting and evaluating endophyte secondary metabolites that have already been discussed elsewhere [4]. Instead, this study will focus on some of the novel lapachol derivatives and their source endophytes, which are paving the way for new therapeutic development opportunities.

2. Endophytes − an insight

Endophytes are a class of microorganisms that inhabit plants naturally without adversely affecting the plant. Among the various endophytes, fungi are of great significance because they are a reservoir of indigenous bioactive compounds. They are ubiquitously present in several plant species capable of colonizing every part of the plant. The applications of endophytic fungi and their bioactives have drastically increased in the past decade with over 1000 research articles published only between 2010 and 2021. They are responsible for the assimilation of nutrients and defense against the host chemicals by synthesizing the required secondary metabolites [4]. In their struggle to survive amidst the host signalling, endophytes produce metabolites that are chemically similar to the ones found in the host plant owing to its symbiotic association [5,6]. Such interactions are more often controlled at the genetic level although certain abiotic factors also contribute to the production. Several studies have demonstrated the antibiotic [7], anti-inflammatory [8], antioxidant [9,10] and anticancer [11] properties of the compounds isolated from these endophytes.

Host plants have specific preferences to a distinctive endophyte that is suggestive of the divergence of endophytic composition. The diversity of fungal species within the host plant is based on the geographic location (temperate, tropic, aquatic and xerophytic) and specific plant part (leaves, twig, seeds and roots). Isolation of endophytic fungi from palm [12], Lichens [13], large trees [14,15], sea grasses [16] have been reported in several studies. Furthermore, studies have been successfully performed to identify and characterize various bioactive metabolites from these endophytes that possess important biological activities. For instance, a breakthrough in this field of research was the identification of Taxol, an anticancer agent, from the endophyte *Taxomyces andreanae* [17]. Further studies on such isolation have led to the identification of an array of such secondary metabolites with bioactive properties. These products can be further scaled for large-scale production without hampering the biodiversity of medicinal plants [9]. An overview of various secondary metabolites and their biological activities are detailed in Table 1.

3. Host-endophyte interaction-a cost−benefit association

Plant-microbe compatibility is the key to a successful endophytic colonization. An endophyte is a microorganism that lives within a host plant, remains symptomless and unobtrusive without adversely affecting the plant [32]. Although the origin of endophytes is not clear, two theories entail the existence of an endophyte-an endogenous theory that states that endophytes were gagged out of the mitochondria and chloroplasts of the plants and an exogenous theory that suggests that endophytes arrived from external environment and got associated with the host plant [33,34]. Yet, one of the most widely accepted phenomenon is the horizontal transmission of endophytic spores from a pool of colonizers that have the potential ability to symbiotically establish itself within the host [35]. Although most such associations are generalistic approach, some of the endophytes have specific affinity for a particular host. The host health is determined by the endophytic community within itself. For instance, stereotypical cacao-specific endophytic communities were established from leaf litter of healthy plants to its seedlings [36,37]. The endophytic community in this case was dominated by *C. tropicale* that was capable of suppressing pathogen damage to the host tissues. The specificity is dictated by the host secondary chemistry. However, in tropical plants, intra-species variation is often not remarkable and goes unnoticed [38]. Yet, the endophytic specificities prevail. The mechanism by which these chemicals are produced is not clearly understood. In addition, it is also not well understood whether these chemicals are produced by the host or the endophyte in response to its interaction with the host [39]. Some of the chemicals produced benefit the host by preventing pathogen attack while some others are produced to facilitate the host tissues against biotic and abiotic stress. Therefore, studies have also suggested that the production of secondary metabolites is a defensive mechanism for the survival of the host plant and its endophyte [40].

Table 1. Various secondary metabolites isolated from different endophytes with their corresponding biological activities.

Metabolite	Fungi	Host plant	Biological activity	Reference
Unspecified compound	*Colletotrichum gloeosporioides*	*Artemisia mongolica*	Antibiotic and fungistatic properties	[18]
Coronamycin	*Streptomyces* sp.	*Monstera* sp.	Antibiotic and antimalarial activity against Plasmodium falciparum	[19]
Campothecin	*Fusarium solani*	*Campotheca acuminate*	Anticancer	[20]
SZ-685C- an anthraquinone	Halorosellinia sp.	Mangrove	Antiproliferative against human breast, prostrate, glioma and hepatoma cancer	[21]
Glioccladicillins A and B	Unknown	Cordyceps-colonizing fungi	Apoptosis via intrinsic and extrinsic pathways in melanoma B16	[22]
anhydrofusarubin and methyl ether of fusarubin	*Cladosporium* sp.	*Cucumis sativus*	Cytotoxic against human leukemia cell line HL-60	[23]
Chaetoglobosin A	*Chaetomium globasum*	*Nymphaea nouchali*	Antimicrobial	[24]
Griseofulvin, cytochalasin D, multiplolides, methyl coumarin, sordaricin, phomenone and xyolide	*Xylaria* sp.	Multiple hosts	Antifungal activity	[25,26]
Phomopsolide A	TC2-085 (unidentified endophyte)	*Geummacrophyllum*	Anti-mycobacterial	[27]
Macrophorin A, ocomacrophorin and deacetoxyyanuthone A	*Gliomastix* sp.	*Phakelliafusca*	Anti-mycobacterial	[27]
Pullularins A	*Pullularia* sp.	*Quercus coccifera*	Antiviral	[28]
8-hydroxy-6,7-dimethoxy-3-methylisocoumarine	*Xylariaceae* sp.	*Quercus gilva*Blume	Alpha glucosidase inhibitory activity	[29]
7-methyl anthraquinone	*Penicillium* sp.	*Limonium tubiflorum*	Immunosuppressive	[30]
Lapachol	*Alternatiaaltermata*	*Tabebuia argentea*	Anticancer, anti-inflammatory, antiviral, antiparasitic	[31]

One such natural bioactive compound produced from endophyte is lapachol (Fig. 1), known for its potential anticancer properties [9]. The first identification of this compound was from the red Lapacho tree ("Pau D'Arco"; *T. impetiginosa*). The traditional use of this tree for the treatment of several diseases such as cancer, malaria, mange trypanosomiasis, eczema, herpes, ulcers, syphilis, bacterial and fungal infections, skin disorders, fevers, stomach and bladder disorders led to several exploratory studies to assess the biological potential and chemical composition of this plant [40]. Lapachol was also isolated from various plants of the Bignoniaceae family including *Tabebuia flavescens*, *T. guayacan* [41], *Kigelia pinnata* [42], *Raderma cherasinica* [43], and *Melloa quadrivalvis* [44]. A synthetic analogue of lapachol obtained via a three-component system comprising of 2-hydroxy-1,4-naphthoquinone, 2-phenylindole and 4-nitrobenzaldehyde exhibited potent anticancer properties [45]. The study evaluated its activity against breast cancer and liver cancer both of which showed potent inhibitory activity against the growth of cancer cells with IC50 values of 6.52 and 12.97 μmol/L, respectively [46]. Furthermore, lapachol production via catalytic hydrogenation demonstrated significant anticancer properties against lung cancer, renal cancer, melanoma, breast cancer, prostrate cancer and ovarian cancer [47]. Further studies carried out by **Xue** et al., demonstrated that lapachol was able to reduce the survival rate of rat brain microvascular endothelial cell [48]. Studies carried out by **Cen** et al., showed auxillary properties of lapachol in interacting with the HIV-1 auxillary protein Vpu thereby inhibiting the viral release [49].

4. Lapachol production from endophytic fungi

Isolation and biological assays on lapachol have been marked as one of the most interesting studies in phytochemistry. Dating back to 1952, Dr. Osvaldo Goncalves de Lima evaluated the antitumor potential of lapachol based on its ability to produce xiloidone in presence of pyramidine. Though synthetic production of lapachol and its isolation from

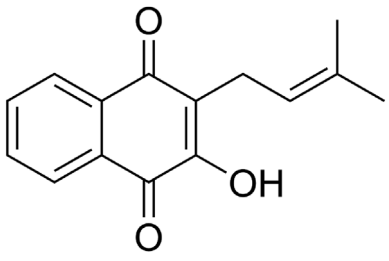

Fig. 1. Structure of the secondary metabolite-lapachol.

plant sources have been well established, bioprospecting of this compound has recent come in light after the study carried out by **Sadananda** et al., [31]. Endophyte bioprospecting research is still in its infancy, with few formulations available at the pharmaceutical market [50]. This first ever report evaluated 13 endophytic fungi from various parts of *Tabebuia argentea* belonging to the bignoniaceae family. Among the different isolates, the study identified *Aspergillus niger* and *Alternaria alternata* as the two potent fungi capable of producing this naphthoquinone known as lapachol. This can be considered as a preliminary study for the isolation and characterization of lapachol-producing endophytes. Further, the study carried out by **Govindappa**, evaluated the antimitotic and antiproliferative potential of lapachol produced from endophytic fungal sources [51]. Among the various parts tested for isolation of fungal endophytes, leaf yielded *A. alternata, Alternaria* sp., *Rhizopus* sp., *Fusarium oxysporum, Fusarium* sp., *A. niger, Penicillium* sp., the bark yielded *A. anlternata, F. oxysporum* and unidentified fungi whereas the stem yielded *A. alternata* and *Alternaria* sp. In this study, lapachol was confirmed to be produced by the leaf endophytes *A. alternata, Penicillium* sp., *Alternaria* sp., and *A. niger,* the bark endophytes were *A. alternata*. Furthermore, lapachol fraction from *A. niger* was proven to possess inhibitory potential against meristematic cells and therefore involved in inhibition of mitotic activity by a series of mechanisms such as chromosomal bridge and clumping, stikiness, abnormal distribution of metaphase chromosome, shrinked interphase cells, chromosomal degeneration, chromosomal bridges with vagrant chromosomes at anaphase, binucleolar and nucleolar burst and mega cell, large nucleolus and chromosomal clumping in small cells [52,53]. The extracted lapachol also demonstrated potent antiproliferative activity against yeast cells up to 70%. This study concluded that the anticancer properties of lapachol was remarkable and could be evaluated through further *in vitro* and *in vivo* experiments to uphold the druggability of the molecule.

In another interesting study *Mucorcircinelloides* NRRL3631, *Botrytis cinerea* UCA992 and *B. cinerea* 2100 were used for the biotrasformation of lapachol. In this study, biotrasformation into avicequinone-A by *M. circinelloides*, 3′-hydroxylapachol by *B. cinerea*, and into dehydro-α-lapachone by both *B. cinerea* and *M circinelloides* were carried out. These compounds were tested for their cytotoxic abilities that showed a higher cytotoxicity exerted by dehydro-α-lapachone over that of lapachol. This compound also revealed to be of lower toxicity to fungal cells suggesting the detoxification potential of the endophyte. A similar biotransformation study was carried out by **Barbosa** et al., that evaluated nine filamentous fungi namely, *A. flavus, A. fumigatus, F. oxysporum, Rhizopus microsporus, Penicillium corylophilum, Paecilomyces variotii, Phanerochaete chrysosporium, Rhizomucor miehei,* and *Trichoderma asperellum* for their ability to transform lapachol into a less toxic and feasible metabolite [54]. The study opens avenues for using such filamentous fungi in the process of biotransformation to efficiently produce bioactive compounds with pharmaceutical significance.

5. Conclusion

The present review is on bioprospecting of lapachol producing endophytes. Lapachol is one of the well known secondary metabolite produced from plants belonging to the Bignoniaceae family. Further, an insight on the biotransformation of this secondary metabolite to render it less toxic and more potent has also been reported from a few studies that establish the biotransformed derivatives to be more potent than lapachol itself. In fact, our research shows that endophytic microbes constitute an underutilised bioresource with unique biological and chemical diversity. They have produced over 100 structurally distinct chemical compounds with a wide range of biological properties. In that, lapachol is one of the most potent metabolite with several biotransformed derivatives identified from endophytic origin. Yet, this review article indicates that only a few species have been studied thus far, implying that a large number of strains remain undiscovered. To fully understand the potential and diversity of bioactive metabolites, rigorous bioguided investigations are required. Investigating the metabolites produced by these and their subtle modifications to enhance their biological role could lead to the discovery of novel natural compounds with novel chemical frameworks for medicinal lead discovery.

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Conflict of interest

There is no conflict of interest.

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