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Review Article

Pharmacological potential of fungal endophytes associated with the genus *Ocimum* L.

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Abstract: Endophytes are a rich source of secondary metabolites such as tannins, phenolics, and alkaloids. Endophytic fungi have potential as antioxidants, antimicrobials, anticancer agents, antidiabetic agents, hepatoprotectants, growth promoters, and immunomodulators. Recent studies have shown that endophytes are a valuable source of undiscovered biomolecules. As a result, endophytic isolates from medicinal plants can be used in the pharmaceutical, industrial, and agricultural sectors. *Ocimum* species, for example, have several medicinal properties and are used in traditional medicine. Fungal endophytes have a strong association with *Ocimum* plants. Previous research has shown that the fungal endophytes of *Ocimum sanctum* produce phytochemicals such as alkaloids, terpenoids, cardiac glycosides, flavonoids, terpenes, and volatile compounds. Additionally, fungal endophytes have a direct impact on the medicinal value of the genus *Ocimum*. This review aimed to discuss the pharmacological properties and diversity of endophytic fungi associated with the genus *Ocimum*.

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1. INTRODUCTION

The genus *Ocimum* come under the family Lamiaceae (mint family). The most commonly known species in this genus include basil, sweet basil, and holy basil. These plants are native to tropical regions of Central Africa and South East Asia, but are now widely cultivated around the world for their culinary and medicinal uses. They are known for their fragrant leaves and can be used in a variety of dishes such as pasta, pizza, and salads. In addition, it has long been used in traditional Chinese and Ayurvedic medicine.

The genus includes approximately sixty-four species, among which *Ocimum basilicum* L. (Rama thulasi), *Ocimum americanum* L. (Lime basil), *Ocimum camporum* Gürke., *Ocimum gratissimum* L. (Clove basil), *Ocimum kilimandscharicum* Gürke., *Ocimum campechianum* Mill., *Ocimum tenuiflorum* L. (*Ocimum sanctum* L. (Holy basil)), etc., are some important species with high medicinal value (Dhama *et al.*, 2021). *Ocimum* is a genus of aromatic perennial herbs and shrubs. The plants in this genus are commonly known as basil. The plants can vary in size, with some species reaching heights of up to 3 meters, while others are more compact and only reach a few inches in height. They have simple, opposite leaves and small, two-lipped, tubular flowers. The flowers are typically white or purple in colour. The stem of

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the plant is usually square-shaped, which is a characteristic of the Lamiaceae family (Nahak *et al.,* 2011).

All species of this genus are highly scented due to the presence of volatile oils such as eugenol (2-Methoxy-4-(prop-2-en-1-yl) phenol), ursolic acid (3-Hydroxyurs-12-en-28-oic acid), carvacrol (2-Methyl-5-(propan-2-yl) phenol), linalool (3,7-Dimethylocta-1,6-dien-3-ol), caryophyllene ((1R,4E,9S)-4,11,11-trimethyl-8-ethylidene bicyclo [7.2.0] undec-4-ene), carvacrol methyl ether, and estragol (1-methoxy-4-(prop-2- en-1-yl) benzene) (Pattanayak *et al.,* 2010). Studies have shown that they possess antioxidant, anti-asthmatic, anti-tussive, anti-malarial, anti-pyretic, anti-inflammatory, anti-diabetic, nematocidal, wound healing, anti-cancerous, cardioprotective and immunomodulatory properties. The essential oil of *Ocimum basilicum* (sweet basil) has been found to have antibacterial, antifungal, and antiviral properties. Additionally, basil has been traditionally used to help with digestion, respiratory issues, and as a pain reliever. The compounds eugenol, linalool, and methyl chavicol present in basil are responsible for its medicinal properties (Pattanayak *et al.,* 2010).

Endophytes are microorganisms, such as bacteria and fungi, that live within the tissues of plants, often without causing any harm to the host plant. These microorganisms can be found throughout the entire plant, including the leaves, stems, roots, and seeds. It can be defined as "*all organisms that asymptomatically colonize the living internal tissues of their hosts during a variable period of time*" (Stone *et al*., 2004). Endophytes are found in many different types of plants, including grasses, shrubs, trees, and medicinal plants. Endophytes are also known to have a mutualistic relationship with plants, where both the endophyte and the host plant benefit from each other's presence. Regardless of the plant organ affected, endophytes and hosts interact in a balanced antagonistic manner. The fungus is always at least relatively virulent, which facilitates infection, whereas the plant host's defence inhibits the growth of fungal invaders as well as diseases (Schulz & Boyle, 2005).

Endophytes have been found to have a variety of beneficial effects on their host plants, such as increased tolerance to abiotic stress (e.g., drought, heavy metals, salinity), improved nutrient acquisition, and increased resistance to pathogens. Some endophytes can also produce secondary metabolites that have medicinal properties (Zhang *et al.,* 2006; Sudha *et al.,* 2016). Research on endophytes is an active area of study, and scientists are still working to understand the full range of their effects on plants and their potential uses in agriculture and medicinal sectors. Studies have shown that *Ocimum* plants can harbour a diverse community of fungal endophytes, including species from the genera *Fusarium, Penicillium*, and *Aspergillus* (Table 1). Some of these fungal endophytes have been found to have beneficial effects on *Ocimum* plants. Studies have reported that fungal endophytes can enhance the secondary metabolism of *Ocimum* plants, which can lead to increase in the production of essential oils and flavonoids (Chowdhary & Kaushik, 2015). It is believed that the presence of associated fungal endophytes directly influences the medicinal properties of the genus *Ocimum*.

This review paper tries to discuss the pharmacological potential and diversity of fungal endophytes associated with the genus *Ocimum.*

2. DIVERSITY

Endophytes have a cosmopolitan distribution. They are a highly diverse group of organisms and reside in almost all tissues of the host plant, like roots, stems, leaves, petioles, flowers, barks, etc. Their diversity depends on certain factors like age of the host plant, atmospheric humidity, and average temperature (Chaeprasert *et al.,* 2010). The genus *Ocimum* were associated with diverse group endophytic fungi (Table 1). Among the various tissue, leaves are more species rich due to their thin cuticle, which aids easy penetration, and the presence of photosynthetic areas with loosely arranged cells. From various age-grouped leaves of *O.*

tenuiflorum, 148 endophytes were isolated (Taufiq & Darah, 2018)., and the highest number of isolates was obtained from old leaves with 39.86%, followed by senescent leaves with 25.00%, mature ones with 22.30%, and younger leaves with 12.48% of the isolation rate.

Table 1. Endophytic Fungal species diversity of the genus *Ocimum*

Name of the host	Fungal endophytes	Reference
Ocimum tenuiflorum	*Colletotrichum lindemuthianum* (Sacc. & Magnus) Briosi & Cavara., *Pleosporales* sp., *Phomopsis archeri* B. Sutton., *Colletotrichum gloeosporioides* (Penz.) Sacc., *Fusarium* sp., *Nigrospora* state of *khuskia oryzae* H. J. Hudson., *Penicillum* sp., *Aspergillus flavus* Link., *Nigrospora sphaerica* (Sacc.) Mason., *Alternaria raphani* J. W. Groves and Skolko., *Curvularia borreriae* (Viegas) M.B. Ellis., *Cladosporium sphaerospermum* Penz., *Phoma glomerata* Wollenw and Hochapf., *Alternaria alternata* (Fr.) Keissl., *Alternaria tenuissima* Samuel Paul Wiltshire., *Aspergillus niger* van Tieghem., *Bipolaris maydis* (Y. Nisik. & C. Miyake) Shoemaker., *Chaetomium coarctatum* Sergeeva., *Curvularia lunata* Boedijn., *Diaporthe phaseolorum* (Cooke & Ellis) Sacc., *Fusarium proliferatum* (Matsush.) Nirenberg ex Gerlach & Nirenberg., *Fusarium solani* Mart., *Fusarium verticillioides* (Sacc.) Nirenberg., *Hypocrea* sp., *Hypoxylon* sp., *Macrophomina phaseolina* (Tassi) Goid., *Meyerozyma guilliermondii* (Wick.) Kurtzman & M. Suzuki., *Penicillium crustosum* Thom., *Rhizoctonia bataticola* (Tassi) Goid.	(Bodhankar, 2014; Chowdhary & Kaushik 2015; Shukla *et al.,* 2012)
Ocimum basilicum	*Phoma eupyrena* (Sacc.) Valenz.-Lopez, Crous, Stchigel, Guarro & J.F. Cano., *Emericella nidulans* G.Winter., *Chaetomium olivaceum* Cooke & Ellis., *Chaetomium globosum* Kunze ex Fries., *Nigrospora oryzae* (Berk. & Broome) Petch., *Alternaria citri* Ellis & N. Pierce, *Alternaria alternata* (Fr.) Keissl.	(Shekhawat & Shah 2013)

3. BIOACTIVE COMPOUNDS

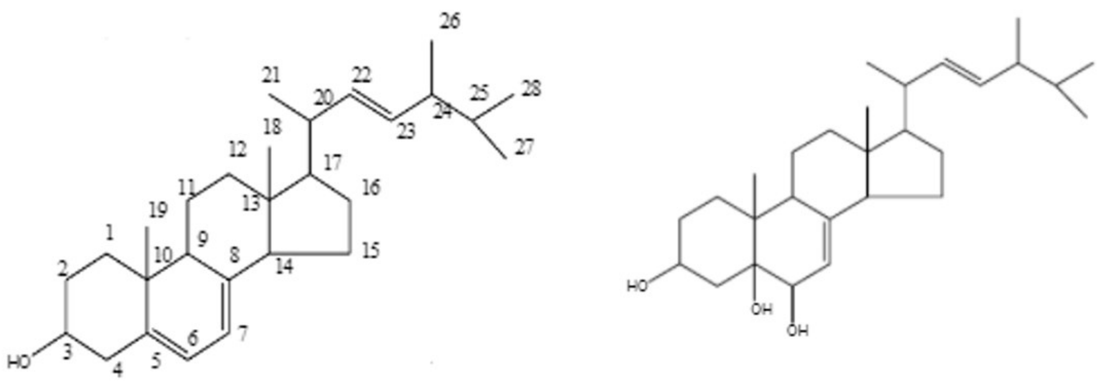
Preliminary phytochemical screening of endophytic fungal crude extract from *O. basilicum* revealed the presence of terpenes, volatile compounds, fatty acids, aliphatic constituents, alkaloids, terpenoids, cardiac glycosides, and flavonoids (Shekhawat & Shah, 2013). Similarly, Gas Chromatography Mass Spectroscopy (GC-MS) chromatogram analysis of the isolate *Macrophomina phaseolina* isolated from the leaves of *O. tenuiflorum* showed the presence of 2H-Pyran-2-one, 5, 6-dihydro-6-pentyl (RT 30.156), hexadecanoic acid (RT 53.017), linoleic acid (RT 64.986), and 10-Octadeconic acid (RT 65.265) (Chowdhary & Kaushik, 2015). Among them, the compound 2H-pyran-2-one is the first report from an endophyte and it exhibited anti-phytopathogenic activity with IC_{50} value of 1.002 and 0.662, respectively, against *Sclerotinia sclerotiorum* (Chowdhary & Kaushik, 2015).

Studies by Mohammad *et al.,* (2015) on the crude extract of endophytes isolated from *O.tenuiflorum,* elucidated the structure of linoleic acid, R (-)-glycerol monolinoleate, 9, 10, 11,-trihydroxy-(12Z)-12-octadecenoic acid, ergosterol, ergosterol peroxide, 1,8-O-dimethylaverantin, coriloxin, and a new natural product named as sactumol. Studies of Gangadevi & Muthumary, (2007) showed that leaf endophyte *Phyllosticta* (sp.6) is a potential producer of taxol in artificial culture media. Similarly, *Nigrospora* sp. isolated from *O.*

basilicum also produces biomolecules such as 5E, 9E-farnesyl acetone, columellarin, totarene, laurenan-2-one, and 8S, 13-cedranediol (Haque *et al.,* 2005).

The endophytic fungal isolate *Penicillium citrinum* from *O. tenuiflorum* was a significant source of bioactive polyketides and alkaloids. The structural elucidation of biomolecules isolated from them reported a new compound (compound 6) (Lai *et al.,* 2013). Phytochemical screening of methanolic crude extract of endophytes from *O. basilicum* has revealed the presence of alkaloids, steroids, terpenoids, and saponins (Abdel-Rahman *et al.,* 2019). Studies of Haque *et al.,* (2005) were able to isolate two sterol compounds from endophytic extract by using silica gel column chromatography with different proportions of mobile phase (ethyl acetate, hexane, and methanol), and their purification resulted two compounds as ergosterol and cerevesterol (Figure 1). Similarly, studies of Shoeb *et al.,* (2013), with HR-ESIMS spectrum analysis of ethyl acetate extract of fungal endophyte revealed the presence of three bioactive compounds such as ergosterol (1), secalonic acid A (2), and secalonic acid D (3) (Figure 2).

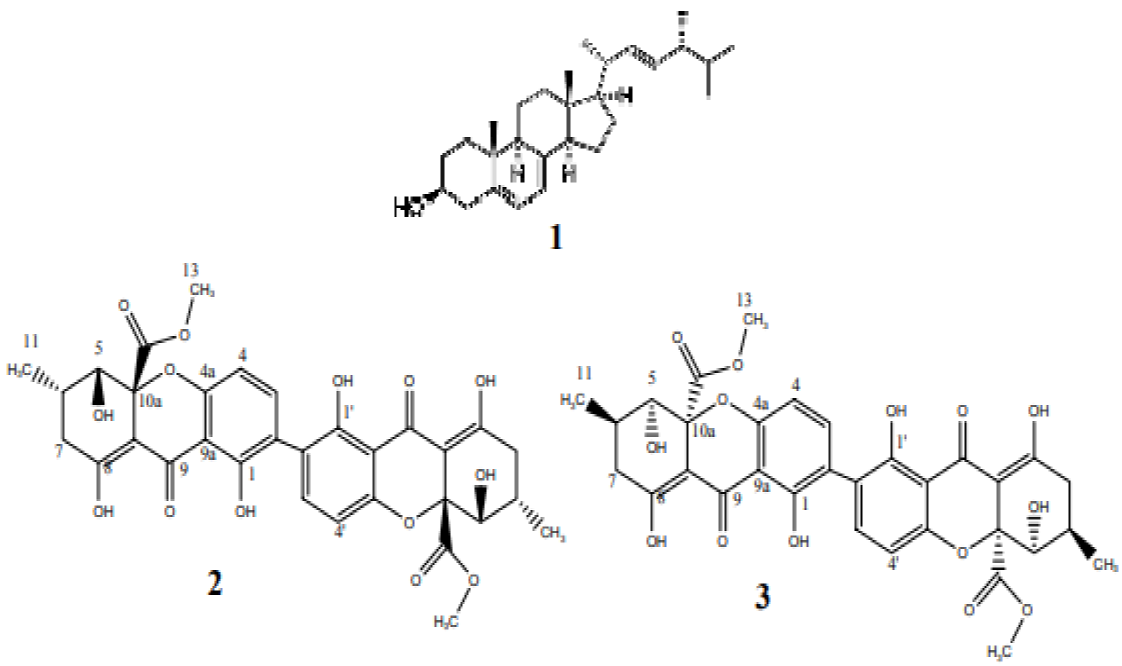
Figure 1. Ergosterol & Cerevesterol



Ergosterol

Cerevesterol

Figure 2. (1) Ergosterol, (2) Secalonic acid A & (3) Secalonic acid D



4. ANTI CANCER ACTIVITY

Silver nanoparticles produced from *Exserhohilum rostrata,* an endophyte from the leaves of *O. sanctum.* By evaluating the anti-cancer potential of this silver nanoparticles showed effective inhibition activity against breast cancer cells (Bagur *et al.,* 2020). Shoeb *et al.,* (2013) evaluated the cytotoxicity of the biomolecules from the endophytes isolated from *O. basilicum* by using MTT assay against a human pancreatic cancer cell line and found that, among the identified biomolecules, secalonic acid A and D exhibited significant anti- cancer activity, with an IC_{50} value of 7.3 and 1.6 mg, respectively Shoeb *et al.,* (2013). Likewise, two compounds (compounds 12 and 17) obtained from the extract of *Penicillium citrinum*, exhibited significant activity against the marine lymphoma cell line L5178Y, with an IC_{50} value of 1.0 and.78 mg/ml, respectively (Lai *et al.,* 2013).

5. HEPATOPROTECTIVE ACTIVITY

The hepatoprotective activities of root fungal endophytic fractions (TRF) 1 (identified as *Paecilomyces variotii*) from *O. sanctum* were evaluated through CCL4 (carbon tetrachloride) induced hepatotoxicity *in vivo* in rats. The results have revealed that the fungal culture filtrate is more potent and significantly reverse the action of carbon tetrachloride induced hepatotoxicity by the restoration of serum AST, ALT, ALP, bilirubin, triglycerides, and protein levels to normal values. It is an indication of stabilization of the plasma membrane as well as repair of hepatic tissue damage caused by CCl4 (Shukla *et al.,* 2012).

6. IMMUNOMODULATORY ACTIVITY

Fungal endophytes from the roots of *O. sanctum* (designated as TRF-1, TRF-2, TRF-3, and TRF-6) were subjected to *in vitro* immunomodulatory activity. The effect of culture extract on the functions of human polymorphonuclear (PMN) cells such as phagocytosis, intracellular killing activity of *Candida albicans*, chemotaxis, and reduction of nitro blue tetrazolium (NBT) dye were evaluated (Madagundi *et al.,* 2013). The result showed that a dose-dependent decrease in the neutrophil was observed with a maximum reduction of 89.78% for TRF-3 and 74.75% for TRF-6, respectively, in the NBT assay. The mean particle amount of phagocytosis of killed *C. albicans* was found to be 7-8 for both TRF-3 and TRF-6, respectively, at 100 g/mL as compared to standard. In the chemotaxis assay, treatment with TRF-3 and TRF-6 showed a maximum number of neutrophils at 100 g/mL, which was comparable with the standard (Madagundi *et al.,* 2013).

7. GROWTH PROMOTING ACTIVITY

Serendipita indica, isolated from the leaves of *O. basilicum,* was tested for its growth enhancing ability on heavy metal contaminated soil. The greenhouse pot experiments under controlled conditions revealed that the culture filtrate treated plants have increased root and shoot dry weight and a decreased concentration of lead and copper in their shoots, but they do not enhance the essential oil content (Sabra *et al.,* 2018). Similarly, Shebany *et al.,* (2013) evaluate the effect of endophytes on the growth and essential oil content of *O. basilicum*. The culture filtrate of *Chaetomium globosum* (isolate no. 1), *C. globosum* (isolate no. 2), *Nigrospora oryzae, Alternaria citri,* and *A. alternata* were used for the study. Application of culture filtrate to the soil, significantly increasing the stem diameter, number of leaves, fresh and dry weight of the plant, and concentration of secondary metabolites such as methyl chavicol, limonene, and total oil content as compared to untreated control plants Shebany *et al.,* (2013).

8. ENZYME ACTIVITY

A study by Kumar *et al.,* (2014) on the endophytes of *O. sanctum* found that 50% of the isolates produced amylase and protease, and 27.5% yielded tyrosinase. Zaidi *et al.,* (2013) evaluated the tyrosinase activity, both qualitatively and quantitatively and found that *Aspergillus* sp. and *Penicillium* sp. (TYR-26, TYR-32, and TYR-38) showed higher tyrosinase activities of 2.8, 3.2, and 2.43 U/ml, respectively. Studies by Shekhawat & Shah, (2013), on extracellular enzyme assays showed that cellulase activity was present with 88.8% of total isolates of endophyte, 77.7% for pectinase, 55.5% for amylase, and 77.7% for tyrosinase.

9. ENZYME INHIBITORS

Culture filtrate of *Phoma* sp., *Eupyrena* sp., *Emericella nidulans* var. *lata,* and *Chaetomium olivaccium* isolated from *O. basilicum* were tested for their anti-amylase activity; all extracts inhibited ($p < 0.01$) alpha amylase. The extracts probably non-competitively bind to the active site of the enzyme. The highest activity was found in *Phoma* with an IC_{50} of 0.108, followed by *Emericella* (IC50 of 0.056) and *Chaetomium* (IC50 of 0.046) at 50g/ml. At 25g/ml, *Phoma* had the highest inhibitory activity with an IC_{50} of 0.083 g/ml (Abdel-Rahman *et al.,* 2019). Likewise, studies of Madagundi *et al.,* (2013) have shown that fungal endophytes of *O. sanctum* were able to inhibit alpha-glucosidase and alpha-amylase. *In vitro* analysis of ethyl acetate extracts of *A. tenuissima* (POST34) and *Trichoderma* sp. (POST047) have demonstrated inhibition against pancreatic-amylase enzyme with IC_{50} values of 27.34 and 40.73 g/mL, respectively Madagundi *et al.,* (2013).

10. PRODUCTION OF SILVER NANOPARTICLES

Extract of *Exserohilum rostra* from *O. tenuiflorum* leaf is used for the preparation of AgNPs and they are evaluated for activities like antibacterial, anti-inflammatory, antioxidant, and anti-proliferative activity in breast cancer cells. The result showed that biomolecules of endophytic extracts capped with AgNPs have a significant level of activity (Bagur *et al.,* 2020).

11. ANTI BIOFILM ACTIVITY

Ethyl acetate extracts of *Lasiodiplodia pseudotheobromae* IBRL OS 64 were evaluated for their anti-biofilm activity against *Streptococcus mutans*. A Congo red agar and a semi-quantitative adherence assay were performed to determine biofilm formation and anti-biofilm activity, respectively. The results have shown that they have good anti-biofilm activity with 89.23% of inhibition for the initial biofilm and 54.14% of inhibition for the preformed biofilm of *S. mutans*. The extracts significantly eliminate the extracellular polysaccharide matrices and hinder the attachment of bacterial cells for biofilm formation (Jalil & Ibrahim, 2021). Similarly, (Bagur *et al.,* 2020) showed the nanoparticle (AgNPs) synthesized from the endophytic fungal extract have the ability of biofilm inhibition against *P. aeruginosa* and *S. aureus*.

12. ANTIOXIDANT ACTIVITY

The ethyl acetate extract of *O. sanctum* root endophyte was subjected to *in vitro* free radical scavenging (2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, hydroxyl radical assay, and reducing power assay, and the isolates TRF-3 and TRF-6 had IC50 values of 271.74 g/mL and 140.54 g/mL for the DPPH (Madagundi *et al*., 2013). In a similar study, it was observed that TRF1 (*Paecilomyces variotii*) had the highest IC50 value at 71.83 g/mL for DPPH and 110.85 g/mL for the hydroxyl radical, respectively (Shukla *et al*., 2012). Fungal endophytes isolated from the roots, stems, and leaves of *Ocimum basilicum* were evaluated for their antioxidant activity and quantitatively determined. The results showed that the IC50 values for DPPH radical scavenging assay were in the following order: *Phoma* (PHE) > *Emericella* (EME) > *Chaetomium* (CHE). The values were 63.3%, 56.2%, and 26.8% at 100 g/mL, respectively. The scavenging activity for hydrogen peroxide of various extracts was in the following order: PHE > CHE > EME, respectively (Abdel-Rahman *et al*., 2019).

13. ANTIMICROBIAL ACTIVITIES

Fungal endophytes were isolated from the leaves of *Ocimum basilicum* and tested against nine human pathogens. The study found that *Nigrospora* (MFLUCC16-0605) exhibited broad-spectrum activity, with minimum inhibitory concentration (MIC) values ranging from 7.81 to 250 g/mL (Atiphasaworn *et al.,* 2017). Similarly, hexane, methanol, and ethyl acetate extracts of *N. oryzae* showed promising levels of activity against *E. coli*, *K. pneumoniae*,*S. aureus*, *S. typhimurium*, *B. cereus*, and *B. subtilis* (Bodhankar, 2014). Compared to the younger leaves of *O. sanctum,* isolates obtained from older leaves have significant antibacterial activity. All the tested isolates showed enhanced activity against at least one of the tested pathogens, and the activity was enhanced after adding water extract of the host plant into the culture medium (Taufiq & Darah, 2019). The extracts of *L. pseudotheobromae* IBRL OS-64 from *O. sanctum* were tested against food-borne bacteria and found that the ethyl acetate extract had antibacterial activity towards all test bacteria with an inhibition zone ranging from 15.0 mm to 26.0 mm (Taufiq & Darah, 2019). Dichloromethane extract of fungal endophytes from the mature leaves of *Ocimum kilimandscharicum* showed significant anti-bacterial activity (Ismail, 2015). Endophytes of *Ocimum africanum* effectively inhibited methicillin-resistant *S. aureus*, *K. pneumoniae*, and *Shigella boydii* (Nur Amalina, 2015). The dichloromethane and methanol extract of the fungal isolate of *Ocimum basilicum* var. *thyrsiflora* leaves displayed the highest antimicrobial activity against the selected bacteria (Omar, 2015).

Studies of Shekhawat & Shah, (2013) evaluated the anti -bacterial potential of five fungal endophytes associated with *Ocimum sanctum* against *E coli*, *Bs megaterium*, *Paeruginosa*, *S marsences*, *B. subtilis*, *S. aureus*, *M.luteus* and *S. typhi*. Among them, the fungal isolate (F GTS 2) significantly inhibited *P. aeruginosa*, and three fungal isolates (F GTS 2, F GTL4, and F GTS 5) significantly inhibited *M. luteus* (Shekhawat & Shah, 2013).

Fungal endophytes isolated from *Ocimum sanctum* were evaluated against *Rhizoctonia solani*, *Fusarium oxysporum*, *Colletotrichum falcatum*, and *Helminthosporium maydis*. A total of nine fungi were isolated, but none of them showed inhibition of mycelial growth (Yadav *et al.,* 2015).

14. CONCLUSION

Research on endophytes is important because these microorganisms can have a wide range of beneficial effects on their host plants, including increased tolerance to environmental stress, disease resistance, and improved nutrient acquisition. Additionally, endophytes have potential for use in agricultural and biotechnology applications, such as the development of biopesticides. Overall, understanding the interactions between endophytes and plants can lead to improved crop yields and sustainable agricultural practices. Endophytes are a rich source of bioactive molecules such as antibiotics, enzymes, and secondary metabolites. These molecules have a wide range of potential applications, including in medicine, agriculture, and industry. Studies showed that numerous biologically active substances can be produced by endophytes of the genus *Ocimum*. They share structural and functional similarities with chemicals made by *Ocimum* plants. Exploiting the pharmacological potential of endophytes will assist the pharmaceutical sector in developing novel, affordable treatments against devastating diseases.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Manikandan Karthika: Wrote the first draft. **Avanoor Ramanathan Rasmi:** Supervision, validation, and correction of the final draft.

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