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REVIEW PAPER

Endophytes – untapped resources and pharmacological prospects against coronaviruses

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ABSTRACT

Introduction and aim. Viral infections stand to be among the most devastating diseases globally. Though significant efforts have been made in research and drug development against viral infections, the search for safe, affordable and effective vaccines against the current ravaging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still on. This is because already approved vaccines still need improvement. This review draws the attention of researchers on the potentials of bioactive substances from endophytes against the novel coronaviruses.

Material and methods. This assessment was made using references of articles published in English peer reviewed journals indexed in PubMed and Google Scholars databases up to June, 2022. The following key words were used; 'coronaviruses', 'Endophytes', 'Endophytes and viral infections, 'Endophytes and COVID-19, 'SARS-CoV'.

Analysis of the literature. *In-silico, in-vitro and in-vivo* studies revealed that natural compounds from endophytes showed antiviral activities against various human coronavirus, including HCoV 229E and a norovirus surrogate, the feline coronavirus FCV F9, COVID-19, Coronavirus 2 (SARS-CoV-2), SARSCoV-2 Mpro, among others.

Conclusion. This finding calls for researchers to also focus on endophytes, as part of drugs development in the bid to finding possible solution in combating the devastating COVID-19, an emerging situation.

Keywords. coronaviruses, endophytes, endophytic fungi, SARS-CoV, natural products

Introduction

Endophytes could be termed as microbes, mainly fungi or bacteria that reside within cells of plant tissues.[1] They have no negative impact on the host plant. They are ubiquitous in all plant species.[2] Besides their beneficial role on host plants through provision of resistance against stress, they also generate molecules of interest against divers diseases including cancer, fungal infections, viral infections, to mention a few.[3,4]

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Transmission of endophytes occurs through seed in the entire plant's life cycle. However, their high nutrient demand may cause them to become parasitic and cause disease to host plants.[5] Studies have revealed the existence of endophytes in every parts of medicinal plant including resins, scales, flowers, roots, barks, stem, canals, leaves and meristems.[6] They can easily be fermented and cultured.[7] They possess the ability to generate natural and potential bioactive compounds.[6]

Several studies have demonstrated endophytes and their specific metabolites to facilitate tumor death.[8] Also an endophytic fungus isolated from the stem of *Tripterygium wilfordii* Hook.f. produced a novel cyclopeptide antibiotic which has related chemical properties as echinomycin.[7,8]

Endophytes have attracted remarkable attention as a result of their capacity to generate innovative bioactives with various biological activities.[1] The uniqueness of endophytes is attributed to their potentials against resistant human and plant pathogens.[9]

In the bid to curb the ravaging SARS-CoV, the discovery and development of more safe, potent and cost-effective antiviral drugs as well as vaccines is very necessary. Although studies have been carried out on the relevance of animal products, medicinal plants, and marine resources against SARS-CoV, no assessment have been done on the potential of natural anti-viral bioactive compounds from endophytes against SARS-CoV.[1,10]

Aim

This review would help accelerate the discovery and development of alternative remedies from endophytes against the current prevailing pandemic, SARS-CoV, COVID-19.

Material and methods

References of articles published in English peer reviewed journals indexed in PubMed and Google Scholars databases up to June, 2022 were assessed electronically using some key words viz; 'coronaviruses', 'Endophytes', 'Endophytes and viral infections, 'Endophytes and COVID-19, 'SARS-CoV'.

Analysis of the literature

Coronaviruses (COVS)

Coronaviruses (from the latin word, *Coronaviridae*) are group of RNA-containing viruses which are sub-divided into two families; *Coronavirinae* and *Torovirinae*.[11] Alpha, beta, gamma, and delta coronaviruses are four genera in the *Coronavirinae* subfamily. Among the human coronaviruses (HCoV-HKU1, SARS-CoV-2, HCoV-NL63, SARS-CoV, HCoV-OC43, HCoV-229E, and MERS-CoV), SARS-CoV-2 appears to be responsible for COVID-19 pandemic.[11,12] They are viruses with non-segmented, single-stranded and positive-sense RNA genome.[11]

Coronavirus pandemic-19 (COVID- 19) is a deadly disease discovered on 31st December 2019, identified as a novel coronavirus 9th January 2020, and declared a public health emergency of international concern on 30th January, 2020.[13,14] It is caused by severe acute respiratory syndrome (SARS-CoV-2), a single-stranded RNA (ssRNA) virus. Thus, the International Committee on taxonomy of viruses categorizes it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[15] Recently, as at May 2022, the World Health Organization report revealed at least 500 million confirmed cases of COVID-19, with more than 6 million deaths worldwide.[16] It is a betacoronavirus that causes several diseases.[15] Out-break of two pathogenic virus, the Severe Acute Respiratory Syndrome (SARS-CoV, or SARS) and the Middle East Respiratory Syndrome (MERS-CoV, or MERS) preceded the Coronavirus pandemic-19 (SARS-CoV-2). The origin of SARS was from Wuhan City, Hubei Province, Southern China in 2002, while MERS has its origin in Jeddah region of Saudi Arabia after infecting a patient in 2012.[12,17,18]

At the end of 2019, a new coronavirus, previously known as SARS-Co-2 was recognized as the cause of pneumonia in Wuhan, a city in the Hubei Province, China.[19] From there, it spread throughout China and other parts of the world. SARS-CoV-2 was labeled by the World Health Organization (WHO) as Coronavirus disease 2019 (2019-nCoV) on 11th March 2020 due to its pandemic nature.[12,20]

Trend in endophytes research

Existence of fungal endophytes inside medicinal plants has shifted the attention of new drugs discovery from medicinal plants to fungi endophytes.[21] Being substitutes for plants secondary metabolites, several bioactive natural products with antiviral, antifungal, antibacterial, antioxidant and cytotoxic properties have been discovered from endophytes of plants, marine and animal origin.[21]

This gap is currently attracting attention of microbiologists, pharmacologists, natural product chemists, biochemists, botanists, biologists and industrialists. This is also attested by the increase in number of endophyte research publications in recent times. Currently, advanced chemical, biotechnological and computational molecular biology methods are being used for significant production of bioactive compounds from endophytes.[22]

Although natural products from medicinal plants[23], animals[24] and marine resources[14,25] have been explored to have potentials against the ravaging SARS-CoV-2, the place of endophytes is still emerging. In this evaluation, potentials of endophytes against the novel COVID-19 virus were addressed through literature survey.

Anti-viral activities of endophytes

Activities against influenza virus

Endophytic fungal extract from mangrove plant, *Aegiceras corniculatum* displayed potent activity against influenza A viral (H1N1). Compounds isolated from the extract include isoindolones (emerimidines A and B, emeriphenolicins A and D) and other compounds, including aspernidines A and B, austin, austinol, dehydroaustin, and acetoxydehydroaustin. Cytopathic inhibition assay showed activity of eight compounds (Table 1) against influenza A virus (H1N1).[26]

Table 1. Anti-influenza activity of endophytes

Endophytic fungi	Host plant/source	Bioactive compounds	Reference
Emericella sp. (HK-ZJ)	*Aegiceras corniculatum*	Emerimidine A and B and Emeriphenolicins A and D	26
Nigrospora sp YE3033	*Aconitum carmichaeli*	6-O-demethyl-4-dehydroxy-altersolanol A, azaphilones, 8,11-didehydrochermesinone B, and (7S)-7-hydroxy-3,7-dimethyl-isochromene-6,8-dione	27
Phoma sp.	*Aconitum vilmorinianum*	14-nordrimane sesquiterpenoid	28
Nigrospora sp. YE3033	*Aconitum carmichaeli*	hydroanthraquinone derivative, 6-O-demethyl-4-dehydroxy-altersolanol A (1), and two new azaphilones, 8,11-didehydrochermesinone B (6) and (7S)-7-hydroxy-3,7-dimethyl--isochromene-6,8-dione (8)	29
Phoma multirostrata XJ-2-1	*Phoma multirostrata* XJ-2-1	Ergocytochalasin A (1)	30

Similarly, the hydroanthraquinone derivatives, 6-O-demethyl-4-dehydroxyaltersolanol A, azaphilones, 8,11-didehydrochermesinone B, and (7S)-7-hydroxy-3,7-dimethyl-isochromene-6,8-dione isolated from the culture extract of *Nigrospora* sp. YE3033 (from *Aconitum carmichaeli*) showed strong antiviral activity against the influenza viral strain A/Puerto Rico/8/34 (H1N1).[27]

A novel rare 14-nordrimane sesquiterpenoid isolated from the endophyte, *Phoma* sp., of the roots of *Aconitum vilmorinianum* displayed antiviral activity by inhibiting the growth of influenza A virus (A/Puerto Rico/8/34, H1N1).[28]

Studies were done on endophytic fungus (Nigrospora sp. YE3033) derived from *Aconitum carmichaeli* (A. *carmichaeli*) that resulted in the discovery of three new compounds (hydroanthraquinone derivative, 6-O-demethyl-4-dehydroxyaltersolanol A (1), and two new azaphilones, 8,11-didehydrochermesinone B (6) and (7S)-7-hydroxy-3,7-dimethyl-isochromene-6,8-dione (8) as well as five already known analogues/existing compounds (2-5 and 7). Anti-influenza viral strain (A/Puerto Rico/8/34 (H1N1) with IC_{50} values of 2.59, 8.35, 7.82, and 0.80 μg/mL, respectively. Compound 7 showed low cytotoxicity. Authors remarked that such compounds are potentials in the development of anti-influenza A virus agent.[29]

Isolation study was carried out on endophytic fungus (*Phoma multirostrata* XJ-2-1) which led to the unique discovery of Ergocytochalasin A (1), an unprecedented merocytochalasan designed through Diels-Alder cycloaddition of a cytochalasin with an ergosterol. Besides the cytotoxicity activity of compound 1 against six cancer cell lines with IC_{50} values between 6.92 to 26.63 μM, *in vitro* immunosuppressive activity against ConA-induced T cell and LPS-induced B cell proliferation, and its antiviral activity against Human dengue virus type 3 (DV3), influenza A virus (H1N1) and respiratory syncytial virus (RSV), was experimented.[30]

Activities of endophytes against other viruses

Among several endophytic fungal strains (*Scopulariopsis fusca, Fusarium equiseti* and *Geotrichum candidum*) from brown alga, *Padina pavonica*, located in the red sea, *F. equiseti* demonstrated the highest antiviral activity against hepatitis C virus (HCV) NS3-NS4A protease, with an IC_{50} value of 27.0 μg/mL. Two diketopiperazines, (cyclo-L-AlaL-Leu and cyclo L-Tyr-L-Pro) and two nucleosides (cordycepin and Ara-A) were discovered following structural characterization (Table 2).[31]

Brefeldin A, a compound from endophytes associated with *Penicillium* sp. FKI-7127 was reported to exhibit potent antiviral properties.[32]

Antiviral activities against herpes simplex virus (HSV) were also reported in fungal extracts of *Phialophora* sp. (No.96-1-8-1), *Nigrospora sphaerica* (No.83-1-1-2), and *Alternaria alternata* (No.58-8-4-1). Two novel heptaketides, (+)-(2S,3S,4aS)-altenuene (1a) and (−)-(2S,3S,4aR)-isoaltenuene, alongside six already existing compounds, (−)-(2R,3R,4aR)-altenuene, (+)-(2R,3R,4aS)-isoaltenuene, 50-methoxy-6-methyl-biphenyl-3,4,30-triol, alternariol (4), alternariol-9-methyl ether, and 4-hydroxyalternariol-9-methyl ether were identified (Table 2).[33]

Fermentation products from the endophytic fungus *Aspergillus versicolor* yielded two compounds which displayed significant activity against tobacco mosaic virus with inhibition rates of 46.4% and 35.4%, which were more potent than ningnanmycin (30.8%), the positive control.[34]

In a related study, they also isolated four new Oryzaeins and five already available orayzaeins from the endophytic fungus, *Aspergillus oryzae*. Compounds 1 and 2 expressing isocoumarins characteristics possessed an unusual 2-oxopropyl group and a rare 3-hydroxypropyl group revealed activity against tobacco mosaic virus.[35]

In another study by Selin and co-workers, endophytic fungi from medicinal plants of Egyptian origin, exhibited substantial antiviral activity against two virus-

Table 2. Endophytes activity against other viruses

Endophytic fungi	Host plant/source	Bioactive compounds	Activity	Reference
Fusarium equiseti	*Padina pavonica*	Two diketopiperazines, (cyclo-L-AlaL-Leu and cyclo L-Tyr-L-Pro) and two nucleosides (cordycepin and Ara-A)	hepatitis C virus (HCV) NS3--NS4A protease	[31]
***Penicillium* sp. FKI-7127**	*Penicillium* sp. FKI-7127	Brefeldin A	antiviral properties	[32]
***Phialophora* sp. (No.96-1-8-1), *Nigrospora sphaerica* (No.83-1-1-2), and *Alternaria alternata* (No.58-8-4-1)**	*Nigrospora sphaerica* (No.83-1-1-2)	(+)-(2S,3S,4aS)-altenuene (1a) and (−)-(2S,3S,4aR)-isoaltenuene, alongside six already existing compounds, (−)-(2R,3R,4aR)--altenuene, (+)-(2R,3R,4aS)-isoaltenuene, 50-methoxy-6-methyl-biphenyl-3,4,30-triol, alternariol (4), alternariol-9-methyl ether, and 4-hydroxyalternariol-9-methyl ether	herpes simplex virus (HSV)	[33]
Aspergillus versicolor	*Aspergillus versicolor*	unusual 2-oxopropyl group and a rare 3-hydroxypropyl group	tobacco mosaic virus	[34]
Aspergillus oryzae	*Aspergillus versicolor*	Oryzaeins A-D (1-4), four new isocoumarin derivatives, along with five known ones (5-9) [unusual 2-oxopropyl group and a rare 3-hydroxypropyl group]	tobacco mosaic virus	[35]
***Pleospora tarda* strain**	*Ephedra aphylla*	Alternariol and alternariol-(9)-methyl	vesicular stomatitis viruses (VSV) and herpes simplex (HSV-2)	[36]
***Phomopsis* sp. CGMCC No. 5416**	*Achyranthes bidentata*	Three unidentified chromanones	HIV-1	[37]

Table 3. Activities of endophytes against coronavirus

Endophytic fungi	Host plant/source	Bioactive compounds	Activity	Reference
Curvularia papendorfii	*Vernonia amygdalina*	Not detected	HCoV 229E and a norovirus surrogate, the feline coronavirus FCV F9	[9]
Aspergillus terreus	Soybeans	Two dereplicated metabolites, aspergillide B1 and 3α-Hydroxy-3, 5-dihydromonacolin L	anti-COVID-19	[40]
Aspergillus versicolor	Sea crab (*Chiromantes haematocheir*)	four novel indolyl diketopiperazines, aspamides A–E (1–4) and two novel diketopiperazines, aspamides F–G (5–6), in addition to 11 existing diketopiperazines and intermediates	Coronavirus 3-chymoretpsin-like protease (Mpro) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	[14]
***Penicillium citrinum* TOPEF34(Pc)**	Phoenix dactylifera (date palm tree roof)	Benzodiazepine alkaloid analogue cydopentin A and B, dehydrocyclopeptin and cyclopeniol	Significant SARS-COV2 Mpro inhibitory effect compared to GC376 as positive control	[44]
***Cladosporium* sp. 7951**	*Paris polyphylla var. yunnanesis.*	Eight new aspulvinone analogues, aspulvins A–H (1–8) and aspulvinones D, M, O, and R (9–12).	All isolates displayed various degrees of inhibitory activity against SARS-CoV-2 Mpro at 10 μM	[47]

es, vesicular stomatitis viruses (VSV) and herpes simplex (HSV-2). Alternariol and alternariol-(9)-methyl were two compounds isolated from endophyte *Pleospora tarda* that showed antiviral property.[36]

From the stems of *Achyranthes bidentata* the fungal strain *Phomopsis* sp., CGMCC No. 5416 were extracted which resulted to three unidentified chromanones, that revealed promising antiviral activities against HIV-1.[37]

Alternaria tenuissima QUE1Se, a fungal endophyte of *Quercus emoryi* was found to exhibit strong anti-HIV activity.[38]

Studies on potentials of endophytes against coronavirus

According to Afra and co-workers, the endophytic fungus (*Curvularia papendorfii*) isolated from *Vernonia amygdalina,* produced antiviral activity against human coronavirus HCoV 229E and a norovirus surrogate, the feline coronavirus FCV F9 (Table 3).[9]

In-silico studies play a significant role in preliminary assessment of potential drugs, which can further be subjected to *in-vitro* and *in-vivo* studies.[39] In-silico assessment of the metabolites produced by the endophytic fungus, *Aspergillus terreus* associated with soybeans against COVID-19 revealed two dereplicated metabolites, aspergillide B1 and 3α-Hydroxy-3, 5-dihydromonacolin L to be potent anti-COVID-19 drug candidates in the molecular docking study.[40] The authors submitted that the potential of Aspergillide B1 and 3α-Hydroxy-3, 5-dihydromonacolin L could be developed as phytopharmaceuticals for the management of COVID-19.

Aspergillus versicolor, an endophyte connected with the sea crab (*Chiromantes haematocheir*) was subjected to isolation study, which led to the discovery of four novel indolyl diketopiperazines, aspamides A–E (1–4) and two novel diketopiperazines, aspamides F–G (5–6), in addition to 11 existing diketopiperazines and intermediates. Computer-aided study on isolates showed activity against coronavirus 3-chymoretpsin-like protease (Mpro) of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Authors submitted that screened molecules could be helpful against corona virus disease-19 (COVID-19).[14] Endophytic fungi could be considered as treasures of unique bioactive metabolites.[41]

Out of 16 alkaloids that previously displayed antimicrobial potential on angiotensin-converting enzyme 2 using molecular modeling and *in silico* studies, *Aspergillus Fumigatoside* E showed best fitting within active sites of angiotensin-converting enzyme 2 (ACE2) which

is an entry receptor in which SARS-COV was transmitted followed by Aspergicin.[42]

A computational study using molecular docking and molecular dynamic simulation revealed pyrrocidine A and dankasterone B, secondary metabolites of endophytic fungi *Acremonium zeae*, as potent inhibitors of viral RdRp. The authors suggested it as a promising and efficient anti-coronavirus drug which can be explored.[43]

The extract of *Penicillium citrinum*, TDPEF34, showed potential inhibition and was further analyzed to identify potential Mpro inhibitors. Following bio-guided isolation, a series of benzodiazepine alkaloids cyclopenins with good-to-moderate activity against SARS-CoV-2 Mpro were identified. The authors posited that their findings could be utilized for further *in vitro* and *in vivo* investigations to produce anti-SARS-CoV-2 drug candidates as well as critical structural information that could be used in future design of potent Mpro inhibitors.[44]

Fonsecin, a naphthopyrone pigment from *Aspergillus fonsecaeus* mutant has shown high binding affinity for SARS-COV-2 PLpro by interacting with the Tyr 268 amino acid residue of enzyme cavity based on *in silico* molecular docking and molecular dynamic studies.[43,45]

The genome of *Penicillium thymicola* contains a polyketide synthase and a nonribosomal peptide synthetase hybrid gene cluster, which upon expression leads to the synthesis of Pyranonigrin A. Pyranonigrin A. is a secondary fungus metabolite with strong inhibitory capability against the SARS-CoV-2 Mpro.[43,46]

Conclusion

As part of drugs discovery and development in the fight against the devastating Corona Virus Disease-19, the search for antiviral metabolites from endophytes is becoming an area of exploration by researchers. The above studies revealed that endophytes are vital sources of natural bioactive compounds which have potential in immunomodulations for the prevention and treatment of CoVs. While addressing the preclinical roles of endophytes against the ravaging virus, cognizance of their clinical trials as well as safety (toxicity profile) should be put into consideration. Further studies still need to be done on their mechanism of actions.

Declarations

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Author contributions

Conceptualization, E.O.E.; Methodology, E.O.E., C.I., C.C.E. and M.M.; Writing – Original Draft Preparation, E.O.E.; Writing – Review & Editing, C.I., G.C.O., C.C.E., M.M. and E.O.E.; Visualization, E.O.E.

Data availability

Data are available from the corresponding author upon request.

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