Therapeutic potentials of endophytes for healthcare sustainability

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ABSTRACT
Morbidity and mortality rates are on the upward trajectory globally, probably due to lack of effective treatments and poor healthcare. Most effective drugs are, however, characterized by serious side effects upon long usage. It is, therefore, imperative to explore natural sources for efficient therapeutics with little or no side effects. This paper outlines the therapeutic potentials of endophytes using published articles on endophytes in both Web of Science (WoS) and Scopus (1990–2020). Scientific evidences discussed in this review suggest endophytic microbes as reservoirs of novel bioactive compounds belonging to the following classes alkaloïd, xanthones, methoxyphenols, depsipeptide, bicyclic lactones, depsidones, butenolides, maleimide-bearing compounds, ergosterol, spirobisnaphthalenes, benzopyran derivatives, isofuranolone, butyroactones, diketopiperazine, sesquiterpenoids, cytochalasin-related compounds, pestalols and cyclic pentapeptides. The identified compounds are characterized by promising therapeutic potentials such as antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic, antiviral, neuroprotective, and hepatoprotective properties, which are significant to healthy living and sustainable healthcare. This review further discusses the emerging potentials of endophytes in the production of antibiofilm, antimultiresistant Staphylococcus aureus (anti-MRSA) and lipase inhibitors (LIs). The prospective applications of endophytes in the development of anti-COVID-19 medications and therapeutics for the management of neglected tropical diseases (NTDs) are also advocated in this review. The therapeutic potentials of endophytes, if properly harnessed, would in no small measure contribute to good health, which is an integral part of the sustainable development goals (SDGs) of the United Nations (UN).

KEYWORDS
Anti-COVID 19; biopharmaceuticals; endophytes; healthcare; therapeutics; sustainable development goals

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Introduction
Endophytes are microbes which grow inside plant tissues [1] and exhibit great biodiversity in nature based on endophyte–plant interactions, endophytic behavior, endophyte–plant association, endolichen-infection, endophytic compartment, endophyte infection, endophytic colonization, endophytic bacteria–algae interactions/association and endophytic competence among others [2]. A text mining of endophytic microorganisms from collections of previous studies revealed diversity of endophytes across bacterial, fungal, yeast, algae and actinomycetes groups.

Endophytic microbes are characterized by the capability to produce varieties of secondary metabolites [3], which have shown significant pharmaceutical potentials such as antioxidant, anticancer, immunomodulatory, antiviral, etc.
antituberculosis, anti-parasite [2,4]. Some of the secondary metabolites produced by endophytes are analogous to that of the host plant while others are non-analogous, hence, they are promising sources of biologically active compounds for drug development [2,5,6] and other industrial purposes [7,8]. In other words, endophytic microorganisms are reservoirs of novel bioactive compounds with prospect in different industrial sectors such as food, agricultural and pharmaceutical [].

Good health and well-being are among the 17 UN SDGs, intended to be achieved by 2030 [9]. However, several people are currently battling with one disease or the other, with little or no effective treatment. In cases where prescribed drugs are efficient, long-term usage of such medications is characterized by serious side effects [10,11] while diseases with no cure are only being managed throughout life. More so, several lives have been lost to different diseases including cancer, diabetes mellitus, hypertension, neurodegenerative diseases, HIV/AIDS and most recently, coronavirus disease 2019 (COVID-19) [12,13]. Undoubtedly, natural bioactive compounds with therapeutic properties are promising candidates for drug development [2] toward treatment and effective management of these diseases. Endophytes have, indeed, shown auspicious potentials for production of metabolites with remarkable therapeutic aptitudes including anticancer, anti-inflammatory, antimalarial, antidiabetic, antioxidant, hepatoprotective, neuroprotective and antiviral [11,14–19]. These can, therefore, be harnessed by pharmaceutical industries for development of medications, which is pivotal to ensuring good health and well-being in the society. Therefore, this paper gives an overview of the therapeutic potentials of endophytes with a view to revealing the emerging and prospective areas of endophytes applications capable of promoting healthcare sustainability, which is a major component of the UN SDGs, designed to achieve an improved and more sustainable future for all by 2030 [].

Methodology
Identification and mining of endophyte resource

The study mined public available endophyte-related research articles in the WoS and Scopus databases from 1990 to 2020 (Tuesday, 07 July 2020, 22:00:05, GMT +1) following the guideline of the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses: PRISMA’ [20]. The database mining was achieved via the term ‘endophyte‘, which optimally retrieved variant indexes (e.g., endophytes, endophytes and endophytic) as title-specific search. The investigation final database was composed chiefly research articles but was devoided of pre-articles and post-publication synthesis such as note, correction addition, meeting abstract, correction, news item, retracted publication, proceedings paper, editorial material, data paper, biographical item, review, letter, book, retraction, book chapter, etc. (Figure 1). The integrity of applied search algorithm was manually validated by assessing the top 20 articles for specificity and efficiency. The articles metadata were all downloaded either as tab-delimited (Win, UTF-8) or comma separated (CSV Excel) file for further processing [].

De-duplication of endophyte-documents and subject classification

The metadata obtained from the two databases in the previous section were hybridized and de-duplicated in a python programming environment using ScientoPy package following the protocol of Ruiz-Rosero et al. (2019) [21]. Topical classification of the therapeutic potentials of endophytes were based on average growth rate or trends of authors-keywords in the review database as described by equation 1:

\[
\text{Topical trend} = \left( \frac{\sum_{i=2017}^{2020} \text{EN}_i - \text{EN}_{i-1}}{2020_e - 2017_s} + 1 \right)
\]

where: topical trend = average growth rate; 2017_s = start year; 2020_e (Tuesday, July 07,
Figure 1. Flowchart for endophyte resource mining and screening for the investigation (1990–2020). The tick arrows and boxes indicate computer-assisted de-duplication stage.
2020, 22:00:05, GMT +1) = end year; ENi = number of endophyte-related research documents in 2017.

The topics considered include antioxidant potential (antioxidant compound, antioxidant potential, antioxidant properties, antioxidant activities); neuroprotective property (anti-acetylcholinesterase, antiacetylcholinesterase, acetylcholinesterase inhibition, cholinesterase inhibition, anti-AChE activities, antia
dutrylcholinesterase; anti-BChE activities, butyrylcholinesterase inhibition); anticancer potential (anticancer, antimitotic, antitumoral, antineoplastic, cancer inhibition, antitumor, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, antiproliferative, antimitotic, 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topic activity, antiviral property, and emerging potentials as discussed in the succeeding sections. Although, there are many documents related to the outlined topics, this review is limited to the most relevant recent studies in the review database as identified by equation 1.

**Therapeutic potentials of endophytes**

This section discusses the scientific evidences that suggest endophytes as reservoirs of novel bioactive compounds with promising therapeutic potentials. Copious natural compounds have been isolated and purified from different endophytic microbes over the years. The therapeutic potentials of such compounds and the respective sources are summarized in Table 1.

**Anticancer property**

Identification of studies on ‘anticancer property of endophytes’ as described by equation 1 returned 287 articles for journals published between 1990 and 2020, out of which 26% were published between 2018 and 2020, implying that the anticancer efficacy of endophyte-derived extracts and compounds are still of research interest. The continued interest in cancer research is not surprising, as cancer is one of the leading causes of death globally.

Cancer research efforts have undoubtedly, yielded positive results as a wide range of natural anticancer compounds have been isolated from different sources including endophytes. Taxol, a popular chemotherapy drug used in cancer treatments, has been isolated from a number of endophytes hosted by plants belonging to *Taxus* and *Taxodium* genera [22–24]. Other taxol-producing endophytic fungi include *Pestalotiopsis versicolor* and *Pestalotiopsis neglecta* [25]. The toxic effect of taxol on various cancer cell lines, including BT220, HEPG2, HLK 210, MCF7, Int 407, HI 16 and HL 251, have been reported [26,27]. Deoxypodophyllotoxin, another anticancer agent, has been isolated and purified from an endophytic *Aspergillus* strain [28]. Deoxypodophyllotoxin is used as a pro-drug in the management of cancer. Ding et al. [29] isolated a cytotoxic alkaloid, chaetoglobosin U from an endophytic fungus belonging to *Chaetomium* genus. The authors confirmed that the bioactive compound ‘chaetoglobosin U’ had toxic effect on ‘human nasopharyngeal epidermoid tumor KB cell line’ with the inhibitory rate correlating with that of the positive control [5-fluorouracil] [30]. A different study by 99, reported the isolation of falcarinol from a *Paecilomyces* species hosted by *Panax*
Therapeutic potential | Endophytes | Bioactive compounds | Reference
---|---|---|---
**Anticancer** | *Fomitopsis* sp. P. Karst | Camptothecine | [33]
| *Alternaria alternate* (Fr.) Keissl | | | |
| *Phomopsis* sp. (Sacc.) | | | |
| *Phomopsis* sp | 1,5-dihydroxy-3-hydroxyethyl-6-methoxycarbonylkanthone; 1-hydroxy-3-hydroxyethyl-8-ethoxycarbonylkanthone | | [40]
| *Alternaria alternate* | Capsaicin; Alternariol-10-methyl ether | | [35]
| *Fusarium* sp. (No. DZ27) | Beauvericin | | [38]
| *Myrothecium roridum* | Myrothecumones A and B | | [41]
**Anti-inflammatory** | *Corynespora cassicola* | Corynesidone A; corynesidone C; corynesidone D and corynether A | [52]
| *Aspergillus* species | Terrusnolides A, B, C and D | | [51]
| *Aspergillus terreus* | Cowabenzophenone A | | [49]
| *Phomopsis* sp. | Farinomalonein H | | [44]
| *Fusarium chlamydosporum* | Chlamydosterols A | | [45]
| *Edenia gomezpompe* | Spiroisbaphthalenes | | [46]
| *Penicillium citrinum* | Benzopyran derivatives | | [19]
| QJF-22 | | | |
| *Boeremia exigua* | Boremexins A, B, C and D | | [47]
| *Phomopsis* sp. S12 | Libertellenone M | | [14]
| *Nodulisporium sp* | Isofuranonaphthalenone | | [59]
| *Aspergillus versicolor* | Aspernolides M | | [60]
| *Streptomyces* sp. Suk10 | Gancidin W | | [58]
| *Fusarium* sp | Fusaripeptide A | | [15]
**Antimalarial** | *Nigrospora oryzae* | (5')-2-cis-4-trans-abscisic acid; 7'-hydroxy-abscisic acid; 4-des-hydroxyl altersolanol A | | [67]
**Antidiabetic** | *Chaetomium globosum* | Flavipin (1,2-Benzenedicarboxaldehyde-3,4,5-trihydroxy-6-methyl) | [75]
| CDW7 | | | |
| *Penicillium* sp. YY-20 | Adenosine; Adenine; 2'-deoxyadenosine | | [76]
| *Penicillium citrinum* | (Z)-7,4'-dimethoxy-6-hydroxy-aurone-4-O-beta-glucopyranoside; (15S,3R,4S)-1-(4'-hydroxy-phenyl)-3,4-dihydro-3,4,5-trimethyl-1H-2-benzopyran-6,8-diol | | [80]
**Neuroprotective** | *Chaetomium globosum* | Cytochalasin-related compounds | [17]
| QW and *Phomopsis* sp. IFB-E060 | | | |
**Antiviral** | *Pestalotiopsis* sp. AcBC2 | Pestalols A, B, C, D and E | [84]
| *Aspergillus tubingensis* | Malformin A1 | [46]
| FJBJ11 | | | |
| *Nigrospora* sp. YE3033 | 6-O-demethyl-4-dehydroxylsolanol A | [83]
| *Phoma* sp | Phomanolide (–)-6-methoxymellein | [16]

It is noteworthy that *Paecilomyces* falcarinol exhibited remarkable *in vitro* antitumor effect against different cell lines [30]. Also, anthracenedione derivatives separated from endophytic fungal strains belonging to *Guignardia* and *Halorosellinia* genera inhibited proliferation of KB and KBv200 cells via apoptotic-related mechanisms [31].

Furthermore, Taechowisan et al. [32] reported the anticancer activity of arylo-marin isolated from an endophytic bacterial strain, *Streptomyces aureofaciens* CMUAc130. Interestingly, the bioactive compound inhibited the growth of ‘Lewis lung carcinoma (LLC)’ in experimental mice through apoptotic mechanism related to reduction in BCL-2 and overexpression of BAX [32]. The cytotoxic effects of extracts from the following endophytes: *Fomitopsis* sp. P. Karst, *Alternaria alternate* (Fr.) Keissl and *Phomopsis* sp. against breast and colon cancer cell lines have been documented. The bioactive compound isolated from the...
extracts, camptothecine (a quinoline alkaloid), exhibited its anticancer activity through inhibition of topoisomerase I. Remarkably, some compounds derived from camptothecine are already being used as therapeutics for different forms of cancers [33]. Camptothecine and its derivatives are believed to account for over 30% marketed anti-cancer drugs [34].

*Alternaria alternate*, obtained from *Capsicum annuum*, has shown dexterity for the production of capsaicin and alternariol-10-methyl ether, which showed cytotoxicity against different cancer cells such as HL-60 cells through initiation of apoptosis [35].

Endophytes are also sources of the anticancer enzyme, asparaginase. Studies have shown that asparaginase from *Colletotrichum sp.* E5T9 effectively inhibited the survival rate of CaCo2 (colon adenocarcinoma) and HepG2 (hepatocyte carcinoma) cells [36,37]. However, beaurovericin, a cyclic peptide purified from *Fusarium sp.* (No. DZ27) has been reported to inhibit KB and KBv200 cells growth by induction of ‘apoptosis’ via amelioration of oxidative stress, release of cytochrome c, upregulation of ‘caspase-9 and −3, cleavage of poly (ADP-ribose) polymerase (PARP)’ and failure of mitochondrial membrane potential [38]. Also, sclerotiorin obtained from *Cephalotheca faveolate* has been shown to stop the proliferation of colon cancer (HCT-116) cells through increased production of BAX, lowered production of BCL-2 and consequently, elevated the amount of cleaved caspase-3, which caused apoptosis of cancer cell lines [39].

Other compounds from endophytes that exhibited cytotoxic activities against various cancer cells include ‘1,5-dihydroxy-3-hydroxyethyl-6-methoxy carbonylxanthone and 1-hydroxy-3-hydroxyethyl-8-ethoxy carbonylxan thone’, which were isolated from *Phomopsis sp* [40], and myrotheciumones A and B from *Myrothecium roridum* inhabiting *Ajuga decumbens* [41]. Moreover, a peptide from *Capsicum annuum* endophyte, EML-CAP3, was reported to show strong antiangiogenic activity in varied experimental conditions, through various molecular mechanisms [42]. The stimulation of angiogenesis is an important step in tumor development. Thus, effective blockage of angiogenesis is believed to be a reasonable approach in the treatment of cancer. Furthermore, phenolic-rich extract from an endophytic fungus, *Aspergillus nomius* disrupted the growth of human breast cancer cell and caused apoptosis [43]. Most of the aforementioned anticancer bioactive compounds from endophytes are alkaloids, xanthones, phenolics, depsipeptides and lactones among others.

**Anti-inflammatory activity**

Of the 88 articles returned by equation 1 on the anti-inflammatory property of endophytes, 60% were published between 2018 and 2020, meaning that the anti-inflammatory capacity of extracts and compounds of endophytic origin is currently attracting research interest. A specific example of such studies reported that compounds isolated from *Phomopsis sp.* SYSUQYP-23, including farinomalein H, displayed high modulatory effects on nitric oxide (NO) generation in ‘lipopolysaccharides (LPS)-induced RAW 264.7 cells’ [44]. The anti-inflammatory potential of chlamydosterols A, an ergosterol separated from *Fusarium chlamydosporum* isolated from the foliage of *Anvilee garcinii* (Asteraceae) has been reported. Chlamydosterols was reported to have shown comparable 5-lipoxygenase inhibitory activity with the standard anti-inflammatory drug, ‘indomethacin’ [45]. More so, spirobisnaphthalenes from *Edenia gomezpompae*, as well as benzopyran derivatives from *Penicillium citri num* QJF-22 exhibited anti-inflammatory activities as evidenced by their potent inhibition of the generation of ‘NO in LPS-induced RAW 264.7’ macrophages [19,46].

Furthermore, boremexins A, B, C and D obtained from *Boeremia exigua*, have displayed anti-inflammatory activity toward NO
generation in LPS-induced RAW264.7 macrophages [47]. Also, libertellenone M from *Phomopsis sp.* S12 exhibited anti-inflammatory capacity in experimental models. Libertellenone M downregulated pro-inflammatory cytokine in LPS-treated macrophages, cleavage of pro-caspase 1 and repressed NF-κB nuclear translocation in macrophages [14]. Just like indomethacin, 1, 4-naphthoquinone derivatives, obtained from an endophytic *Talaromyces* species, significantly inhibited ‘LPS-induced NO production in RAW 264.7 cell lines’, as evidenced by inhibition of cyclooxygenase-2 (COX-2), inducible NO synthase (iNOS) and (COX-2) mRNA expressions, as well as reduction of the levels of pro-inflammatory factors interleukin-1β, IL-6, and TNF-α [48].

Other compounds of endophytic sources, which have displayed anti-inflammatory activity *in vitro* include cowabenzophenone A from *Aspergillus terreus* residing in *Bruguiera gymnorrhiza*, desmethyldichlorodiaportintone from an *Ascomycota* species hosted by *Pluchea indica* [49,50] and terrusnolide A, B, C, and D isolated from *Aspergillus* species hosted by *Tripterygium wilfordii* [51]. Others include corynesidone A, C, and D and corynether A isolated from *Corynespora cassicola*, which caused concentration-dependent reduction of ‘LPS-induced TNF-α and iNOS in RAW264.7’ cells [52]. It is worthy of note that majority of the listed (Table 1) endophytic bioactive compounds with anti-inflammatory activities belong to the following classes: depsideoes, butenolides, maleimide-bearing compounds, ergosterol, spirobisnaphthalenes, depsidones and benzopyran derivatives.

**Antimalarial activity**

From the identification of studies on the antimalarial activity of endophytes by equation 1, 30 publications were retrieved with ‘antimalaria’ as the key word while seven articles were retrieved with ‘antiplasmodia’ as the key word. Of the thirty publications on antimalaria, 20% were published between 2018 and 2020 while for the seven studies published on antiplasmodial activity, 33% were published between 2018 and 2020. From these studies, various endophytic isolates were reported to exhibit antiplasmodial activities [53–57]. A specific example of antiplasmodial compounds include the cyclodepsipeptide, fusaripeptide A, isolated from an endophytic fungus inhabiting *Mentha longifolia*. Fusaripeptide A exhibited remarkable anti-*Plasmodium falciparum* (D6 clone) activity [15]. In another study, the compound, ‘3-(2-Hydroxypropyl) benzene-1,2-diol’ purified from an endophytic fungal strain was reported to have displayed anti-plasmodial activity against the multidrug-resistant K1 clone, using dihydroartemisinin as the standard drug [55].

Moreover, gancidin W, separated from an endophytic bacterial strain (*Streptomyces* sp. SUK10) hosted by *Shorea ovalis*, displayed antimalarial activity against *Plasmodium berghei* PZZ1/100 *in vivo*, causing about 80% parasite growth suppression in male ICR mice strain at 6.25 and 3.125 μg/kg.b.wt [58]. Isofuranonaphthalenone purified from *Nodulisporium sp.* residing in *Antidesma ghaesanbilla*, has also shown inhibitory activity against ‘multidrug resistant *P. falciparum* K1 strain’, as assayed using the micro-culture radioisotope technique [59]. Likewise, aspenolides M, obtained from an endophytic fungus belonging to *Aspergillus* genus, displayed activity against *P. falciparum* [[(W2, Indo-China) and (D6, Sierraleone)] [60].

Furthermore, the compound, ‘3-hydroxy-1-(4-(13-(4-(3-hydroxy-3-phenylacryloyl) phenyl) tridecyl)-phenyl)-3-phenylprop-2-en-1-one’ from *Streptomyces sp.* BJSG4 isolated from *Kalanchee pinnata* (Lam.) Pers revealed in vitro activity against *P. falciparum* (Clone 3D7) [61]. Besides, the cyclohexadepsipeptide, pullularin A from *Pullularia sp.* (BCC 8613), has exhibited activity against *P. falciparum* K1 strain [62]. This review suggests that members of the isofuranonaphthalenones, butyrolactones,
diketopiperazine and cyclopsipectides may be promising candidates for development of anti-malarial drugs.

**Antidiabetic property**

The antidiabetic activity of a number of endophytic extracts and compounds have been reported by various studies [63–65]. The search on the antidiabetic activity of endophytes using ‘antidiabetic’ as the key word in equation 1 returned 33 items, 39% of which, were published between 2018 and 2020. ‘Glucosidase inhibition’ and ‘amylase inhibition’ together returned 8 items, of which, 50% were published between 2018 and 2020. From some of these studies, the endophytic *Aspergillus awamori* isolated from *Acacia nilotica* was reported with the ability to produce an uncharacterized peptide with alpha glucosidase and alpha amylase inhibitory activities [66]. The extract and the compounds: ‘(S)-(+)2-cis-4-trans-abscisic acid, 7’-hydroxy-abscisic acid and 4-des-hydroxy altersanol A’ obtained from *Nigrospora oryzae* hosted by *Combretum dolichopetalum* were reported to exhibit ability to reduce the fasting blood sugar of alloxan-induced diabetic mice [67]. Also, peniiisoucomarins C, G and I, obtained from *Penicillium commune* QOF-3, have exhibited strong inhibitory activity against alpha-glucosidase [68].

**Antioxidant activity**

The antioxidant activity of endophytes has attracted much research interest as database search using ‘antioxidant’ as the key word in equation 1 returned 462 items, of which, 41% were published between 2018 and 2020. Scientific findings revealed that endophytes are potential sources of novel natural antioxidant compounds [69,70]. Specific example includes the methanolic extract of *Xylaria sp*. YX-28, an endophyte inhabiting *Ginkgo biloba*, which exhibited notable antioxidant activity in β-carotene-linoleic acid and 2,2-diphenyl-1-picrylhydrazyl (DPPH) antioxidant model systems [71]. Ethyl acetate extract of *Eugenia jambolana* endophyte exhibited significant antioxidant activities as revealed by DPPH and hydrogen peroxide scavenging abilities, as well as ferric reducing power [72]. The antioxidant activity of graphis lactone A from endophytic *Cephalosporium sp*. IFB-E001, isolated from *Trachelospermum Jasminoides*, has been established using DPPH, hydroxyl radical, linoleic acid and human low-density lipoprotein (LDL) experimental models [73].

More so, the antioxidant activity of the ethanolic extract (majorly containing luteolin) from the endophytic *Aspergillus fumigates* of *Cajanus cajan* has been reported. The extract displayed potent antioxidant ability as evaluated by OH radical scavenging, DPPH, reducing power and xanthine oxidase inhibitory and lipid peroxidation assays. The extract also protected DNA from oxidative damage and significantly increased the expression of catalase (CAT), superoxide dismutase (SOD) and glutathione reductase (GR) activities in HepG2 cells [74]. Likewise, flavipin, purified from *Chaetomium globosum* CDW7, has also been reported to possess antioxidant activities and its level determined the antioxidant activity of the crude extracts obtained from the endophyte [75]. Adenosine, adenine and 2’-deoxyadenosine from a *Penicillium* species hosted by *Ginkgo biloba* have also exhibited potent antioxidant activities [76].

**Hepatoprotective activity**

Of the 5 research items published on the hepatoprotective potentials of endophytes between 1990 and 2020, 3 (60%) were published between 2018 and 2020. Examples from these studies include ‘*Ocimum sanctum*’ Linn. endophytic fungal fraction’, which at 200 mg/kg p. o., significantly upturned the effects of carbon tetrachloride (CCl4)-induced
hepatotoxicity, by normalization of serum aspartate transaminases (AST), alanine transaminases (ALT), alkaline phosphatase (ALP) and hepatic damage biomarkers relative to CCl$_4$-treated group. Restoration of altered lipid peroxidation, glutathione (GSH) and CAT by the fungal extract suggest that the hepatoprotective effect is possibly via the antioxidant action of the extract [77]. The ethyl acetate extract of *Achaetomium sp.* hosted by *Euphorbia hirta* has been reported to protect against CCl$_4$ induced toxicity in HepG2 cells as evidenced by 72.13% of cell viability at a concentration of 150 mg/mL compared to 93.26% cell viability reported for the standard, silymarin [78].

The protective effects of ethyl acetate and n-butanol fractions obtained from *Preussia sp.* PPV3.6 (APLF-2), an endophyte isolated from *Andrographis paniculata* leaves, on paracetamol- and ethanol-induced hepatotoxicity have also been reported as evidenced by their capacities to alter serum hepatic damage biomarkers, total cholesterol and triglycerides relative to paracetamol- and ethanol-treated groups. The extracts also restored lipid peroxidation, SOD and CAT levels in treated animals [79]. The hepatoprotective properties of two fungal endophytes (APLF-1 and APLF-2) isolated from *Andrographis paniculata* leaves against CCl$_4$-induced hepatotoxicity have also been reported [79].

**Neuroprotective activity**

Various key words related to neuroprotection were used in equation 1 to search studies on endophytic-related neuroprotective activities in the review collection. These key words include ‘neuroprotective’ and ‘acetylcholinesterase inhibition’. Of the 22 items returned for ‘acetylcholinesterase inhibition’, 44% were published between 2018 and 2020 while for ‘neuroprotective’, 6 items were returned, of which, 75% were published between 2018 and 2020. An example of such studies is the work of 97, where ‘(Z)-7,4’-dimethoxy-6-hydroxy-aurone-4-O-beta-glucopyranoside and (1S,3R,4S)-1-(4’-hydroxyl-phenyl)-3,4-dihydro-3,4,5-trimethyl-1 H-2-benzopyran-6,8-diol’ purified from *Penicillium citrinum*, a *Bruguiera gymnorrhiza* endophyte, exhibited potent neuroprotection against 1-methyl-4-phenylpyridinium-induced oxidative damage in PC12 cells [80]. Another study reported the neuroprotective effect of the fungal endophytic extracts as evidenced by suppression of neuroinflammation (reduced NO production without compromising cell viability) [80], as well as suppression of the expression of the proinflammatory cytokines (IL-6 and TNF-α) in lipopolysaccharide (LPS)-stimulated BV2 microglia cells [81].

Furthermore, the ethyl acetate extract and some of the compounds isolated from the endophytic fungus, *Alternaria alternate*, exhibited potential neuroprotective activities in glutamate induced-PC12 alternate. Also, cytochalasin-related compounds isolated from the endophytes of *Chaetomium globosum* WQ and *Phomopsis sp.* IFB-E060 have been reported to exhibit neuroprotective effect by inhibiting H$_2$O$_2$/MPP$^+$-induced damage in PC12 cells, increasing cell viability and decreasing the amount of lactate dehydrogenase released from the damaged cells [17].

**Antiviral property**

The search of the selected databases on the antiviral potentials of endophytes with ‘antiviral’ as key word in equation 1 returned thirty-six studies (22% of which, were published between 2018 and 2020); ‘anti-HIV’ as key word returned eight studies (only one of which, was published between 2018 and 2020) while ‘anti-HCV’ (anti-hepatitis C virus) and ‘anti-influenza activity’ returned four
studies, 2 of which, were published between 2018 and 2020.

On anti-influenza potentials of endophytic products, 6-O-demethyl-4-dehydroxyaltersolanol A (an hydroanthraquinone derivative) and other compounds isolated from the fermentation product of Nigrospora sp. YE3033, an endophytic fungus inhabiting Aconitum carmichaeli were reported to exhibit retarding effects on influenza viral strains including A/Puerto Rico/8/34 (H1N1), indicating the potential of these compounds as anti-influenza A virus agents [83]. Also, phomanolide (-)-6-methoxymellein, isolated from the fermentation culture of Phoma sp. from Aconitum vilmorinianum roots, has been reported to show antiviral activities against the same strain of influenza A virus [16]. Similarly, pestalols A, B, C, D, and E and other compounds purified from Pestalotiopsis sp. AcBC2, residing in Aegiceras corniculatum, exhibited inhibitory effects against Influenza A virus (H3N2) and Swine Flu (H1N1) [84]. Pulmonary A from Pullularia sp. BCC 861 was reported to exhibit among other activities, antiharpen simplex virus type-1 activity [62] while the extract of Chaetomium globosum JN711454 was reported to exhibit activity against herpes simplex virus type -2 [85]. Furthermore, the sesquiterpenoids, brasilamides B, C, and D, isolated from the fermentation broth of the endophytic fungus, Paraconiothyrium brasiliense Verkley inhibited ‘HIV-1 replication’ in C8166 cells [86]. Malformin A1, a peptide obtained from Aspergillus tubingensis FJBJ11, an endophytic fungus of Brucea javanica (L.), displayed effective inhibitory activity against the infection and multiplication of the tobacco mosaic virus, indicating the potentials of endophytic products as new viricide [46].

**Emerging potentials of endophytes**

In this section, we highlight the emerging potentials of endophytes in the production of antibiofilm metabolites and bioactive compounds with inhibitory effects on multi-resistant *Staphylococcus aureus* (MRSA) and lipase. These traits are regarded as emerging in endophytes because majority of these attributes have only been reported recently with very limited studies.

**Antibiofilm potential**

Biofilm formation is one the various means by which bacteria evade antibiotics, disinfectants and biocides. Biofilms constitute a menace in infection treatment, giving rise to antibiotic resistant pathogens as well as chlorine-resistant bacteria in water and wastewater treatment plants and distribution systems. Table 2 lists emerging applications of antibiofilm potentials of endophytic microbes and their host organisms. Antibiofilm potentials of endophytic strains have possible applications across a wide range of biotechnological sectors include antibiofilm therapeutics/biomedical application (Rajesh and Ravishankar 2014) [87,88,89], antifouling/environmental application [90], application in management of diabetes [91], hydrocarbons cleaning [92], oral and dental antibiofilm therapeutics application [93], and agricultural/environmental applications [94].

Rajesh and Ravishankar (2014)[95] demonstrated antibiofilm potentials of *Bacillus firmus* PT18 and *Enterobacter asburiae* PT39 isolated from *Pterocarpus santalinus* Linn. against *Pseudomonas aeruginosa* PAO1, which may be exploited for antibiofilm medical application. Endophytic *Euroti um chevalieri* KUFA 0006, isolated from *Rhizophora mucronate*, also inhibited biofilm formation in *Staphylococcus aureus* ATCC 25,923 and *E. coli* ATCC 25,922 [90]. *Zingiber officinale* associated *Nocardiopsis* sp shown a dose-dependent biofilm inhibition in the clinically relevant pathogen such as *Staphylococcus capitis* 267 and *S. haemolyticus* 41 strains, with >90% efficiency [89]. Hence, bioactive compounds from *Nocardiopsis* sp extract may be promising candidates for antibiofilm biomedical applications [89]. Possible applications of antibiofilms from endophytes
in the management of diabetic conditions has been reported. For instance, _Alternaria destruens_ hosted by _Calotropis gigantea_ co-concurrently possessed alpha glucosidase inhibiting potentials [91]. _Alternaria destruens_ antibiofilm activities against the copious biofilm producing _S. enterica, E. coli, C. albicans_, and _P. aeruginosa_ have been reported [91].

The antibiotic bioactives from endophytic microbes are diverse in nature. Some of which include enzymes: AHL lactonase [88,95] anthranilic acid derivative; acetylquestinol prenylated indole 3-carbaldehyde derivatives; isochromone derivative [90]; trans cinnamic acid [89]; phenolics [87]; glycolipid biosurfactant [92] and fatty acid [93].

### Table 2. Emerging applications of endophytic antibiofilm.

| Endophytic strain | Host | Target microorganism | Active compound | Biotechnological applications | Reference |
|-------------------|------|----------------------|-----------------|-------------------------------|-----------|
| _Bacillus firmus_ PT18 and _Enterobacter asburiae_ PT39 | _Pterocarpus santalinus_ Linn., | _Pseudomonas aeruginosa_ PAO1 | AHL lactonase | Antibiofilm therapeutics/ biomedical application | [96] |
| _Eurotium chevalieri_ KUFA 0006 | _Rhizophora mucronata_ | _Staphylococcus aureus_ ATCC 25923 and _E. coli_ ATCC 25922 | Acetylquestinol prenylated indole 3-carbaldehyde derivatives, anthranilic acid derivative, isochromone derivative, emodin, physcion, questin, questinol, (11S, 14R)-cyclo (tryptophylvalyl), preechinulin, neoechinulin E, echinulin and eurowcrostaterine | Anti-biofouling /environmental application | [91] |
| _Nocardiopsis sp_ | _Zingiber officinale_ | _Staphylococcus capitis_ 267 and _S. haemolyticus_ 41 strains (more than 90% efficiency) | Phenol, 2,4-bis (1,1-dimethylethyl) and trans cinnamic acid | Antibiofilm therapeutics/ biomedical application | [90] |
| _Enterobacter aerogenes_ VT66 | _Ventilago madraspatana_ Gaertn | _P. aeruginosa_ PAO1 | AHL-lactonase | Antibiofilm therapeutics biomedical application | [89] |
| _Alternaria destruens_ | _Calotropis gigantea_ | _P. aeruginosa, C. albicans, E. coli and S. enterica_ | Alpha glucosidase inhibitors | Application in management of diabetes | [92] |
| _Eupenicillium sp._ and _Aspergillus nidulans_ | _Acacia nilotica_ Linn. | _Streptococcus mutans_ and _Candida albicans_ (51.49% - 79.53% efficacy) | Phenolic compounds | Antibiofilm therapeutics Biomedical application | [88] |
| _Burkholderia sp._ | _Artemisia nilagirica_ (Clarke) Pamp _Coriandrum sativum_ | _Staphylococcus aureus_ (MTCC 1430) | Glycolipid biosurfactant fatty acid | Metabolism of hydrocarbons Oral and dental antibiotic therapeutics application | [93] |
| _Arthrographis kalrae_ | _Streptococcus mutans_ | _Candida albicans_ | - | Agricultural/ environmental applications | [94] |
| _Frankia sp._ DDNSF-01 and _Frankia casuarinae_ DDNSF-02 | _Casuarina spp_ | _Pseudomonas sp._ and _Candida sp_ | - | - | [95] |
Production of anti-MRSA compounds

Even though, *S. aureus* is part of our natural microbiota, it occasionally poses a threat to human lives as a pathogen and ‘a leading cause of hospital and community-acquired infections’ [96]. *S. aureus* is one of the most stubborn pathogenic bacteria, perhaps, due to its multi-drug resistance phenotypic traits, which obviously frustrates the effectiveness of antibiotics treatment. However, recent studies have isolated and identified bioactive compounds capable of inhibiting the growth of MRSA from endophytic microbes. Oxysporone and xylitol, purified from *Heritiera fomes* endophytic fungus, *Pestalotia* sp. have shown remarkable inhibitory activity against six strains of MRSA [97]. Likewise, El-Gendy et al. [98] have reported the efficacy of two metabolites from endophytic Streptomyces strains in the inhibition of a wide range of methicillin-resistant *S. aureus*.

Sources of novel lipase inhibitors (LIs)

Obesity is a considerable public health concern globally, probably, due to its association with several comorbidities, which vividly upsurge ‘morbidity and mortality’ risk in people with obesity [99]. Also, the incidence of obesity is on the increase in various developed nations. In fact, several obese people are living with frustration as all efforts to reduce their body mass index (BMI) through physical exercises have consistently proved abortive. Consequently, they are desperately in search of effective medications and weight loss strategy. It is intriguing that LIs may be a good alternative for such people as LIs are promising drug candidates for obesity and overweight therapy. LIs function by reducing the absorption of dietary fats in the intestine. This occurs when LIs competitively bind to lipase to prevent the breakdown of triglycerides into monoglycerides and fatty acids. Hence, LIs are capable of causing significant weight loss in obese patients [100] and as such, reducing the risk of complications such as type-2-diabetes and cardiovascular diseases. It is, therefore, important for researchers to continue to search for natural compounds with significant ability to inhibit lipase.

Interestingly, endophytes have recently been reported as promising sources of novel LIs. A ginger endophytic actinobacterial strain produced secondary metabolites with promising pancreatic lipase inhibitory activity as the percentage inhibition (≈ 90%) was significantly higher than ginger extract (≈ 69%) and standard LI (orlistat), which had approximate inhibition rate of 88% [101]. The significant lipase inhibitory activity displayed by the endophytic bacterial strain may be linked to the presence of ‘terpenoids, phenols, tannins, flavonoids, alkaloids, and saponins’ in the endophyte [101]. Similarly, cytosporone B and dothiorelone A, isolated from an endophytic fungus, *Phomopsis* sp. exhibited impressive lipase inhibitory activity as the bioactive compounds had higher IC$_{50}$ values than orlistat, used as the standard LI [102].

Future perspectives

Drug development for coronavirus disease 2019 (COVID-19)

COVID-19, caused by ‘severe acute respiratory syndrome coronavirus (SARS-CoV-2)’, is a global public health concern with disturbing impacts on human race. As of 5:15 pm CET, February 15, 2021, there have been over one hundred and eight million confirmed cases of COVID-19 with about two million, three hundred and eighty-one thousand, two hundred and ninety-five deaths reported worldwide [103]. At the moment, however, there exists no World Health Organization (WHO)-approved drug for the treatment of the disease. Hence, all hands must be on deck to search for potential COVID-19 medications.

Spike glycoprotein and 3CL protease are crucial in the pathogenesis and virulence of
SARS-CoV-2 [104]. Thus, inhibition of these proteins is a promising COVID-19 drug discovery strategy. There are ongoing research efforts toward finding novel compounds capable of competitively inhibiting either or both CoV-2 proteins from binding its normal substrate. Molecular docking of natural antiviral compounds found in Chinese medicinal plants against spike glycoprotein and 3CL revealed some interesting results [105], thereby suggesting medicinal plants as promising bioresources for natural anti-COVID-19 compounds. Consequently, endophytes from anti-COVID-19 medicinal plants are capable of producing bioactive compounds with promising CoV-2 proteins inhibitory activity as endophytic microbes are known for secreting secondary metabolites analogues to the host plants. Therefore, endophytes from medicinal plants with confirmed antiviral properties can be explored for isolation of novel compounds with SARS-CoV-2 spike glycoprotein and 3CL protease inhibitory activity. We, thus, suggest that researchers should harness the enormous antiviral potential of endophytic microbes for the discovery of novel anti-COVID-19 drug candidates.

**Promising bioresources for the development of NTDs therapeutics**

NTDs are a wide range of communicable diseases with prevalence in the tropics and subtropics environments in over 140 countries [106]. There are about 18 diseases categorized by the WHO as NTDs, which include among others trachoma, buruli ulcer, leprosy, Chagas disease, leishmaniasis, human African trypanosomiasis and schistosomiasis. According to WHO, NTDs affect over one billion individuals with a huge cost implication on the developing countries annually. In an attempt to prevent, control, eliminate and eradicate NTDs, the WHO developed a roadmap which suggested preventive chemotherapy and the need to strengthen the management of NTDs as some of the major strategies [107]. It is, therefore, noteworthy that bioactive compounds from endophytes have exhibited significant anti-leishmanial, antitrypanosomal and schistosomicidal activity [108–111], which suggests that secondary metabolites from endophytes are prospective candidates for the management of NTDs. However, endophytes are currently underexplored for production of potential drug candidates in the management of NTDs. As such, future research efforts should be geared toward this direction as endophytes are promising bioresources for novel natural bioactive compounds for NTDs therapeutics.

**Conclusion**

Endophytes have unarguably, shown great potentials for production of novel natural bioactive compounds of health significance. More so, endophytic microbes have recently emerged as natural sources of anti-MRSA compounds and LIs. Nevertheless, the promising antiviral potential of endophytes should be properly harnessed for the discovery of novel anti-COVID-19 drug candidates meanwhile, endophytes are waiting to be explored for the development of NTDs therapeutics. Given the diversity of endophytes and the characteristic biotechnological potentials in therapeutics development, endophytes are capable of contributing significantly toward ensuring good health and well-being, which are major elements of the UN SDGs.

**Disclosure statement**

Authors declare that they have no conflict of interest.

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