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Review Article

Potentials of Endophytic Fungus Untapped, including Novel Bioactive Compounds

Kavya Shree Basappa[1], Sri Raghava[2], Sharan Umesha[1,*]

[1]Department of Biotechnology, University of Mysore, Manasagangotri, Mysore, Karnataka, INDIA
[2]Department of Biotechnology, Karnataka State Open University, Muktagangotri, Mysore, Karnataka, INDIA

ABSTRACT

Endophytic fungi have attracted a lot of attention over the past century because of their capacity to produce novel bioactive chemicals with a variety of biological properties, which are then used for medical, pharmacological, and agricultural purposes. Endophytic fungi maintain the physiological and ecological characteristics of the host plant by living inside the plant tissues without causing any disease symptoms. Innovative lead chemicals created by endophytic fungus, such paclitaxel and penicillin, cleared the path for the investigation of new bioactive compounds for industrial application. These bioactive substances are classified as alkaloids, peptides, steroids, terpenoids, phenols, quinones, phenols, and flavonoids, among other structural groupings. The current review is concerned with the importance of endophytic fungi in creating novel bioactive substances with a range of biological properties, such as antibacterial, antiviral, antifungal, antiprotozoal, antiparasitic, antioxidant, immunosuppressive, and anticancer effects. The antibacterial and antiviral properties of endophyte-produced metabolites against human infections are highlighted in this review. It also emphasizes how important it is to use these substances as possible cures for major, life-threatening infectious diseases. The need to intensify the search for new, more effective and affordable antimicrobial medications is motivated by the fact that various results have suggested that these bioactive chemicals may considerably contribute to the fight against resistant human and plant infections.

Keywords: Endophytic fungi, Paclitaxel, Penicillin, Bioactive compounds, Antimicrobial drugs.

Correspondence:
Dr. Sharan Umesha
Professor, Department of Studies in Biotechnology, University of Mysore, Manasagangotri,
Mysore-570006, Karnataka, INDIA
Email: su@appbot.uni-mysore.ac.in; pmumesh@gmail.com

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INTRODUCTION

There has been a significant change in recent years toward a more natural, eco-friendly, and sustainable way of life. According to a majority of academics, antibiotic resistance is rising alarmingly and becoming a major global issue, rendering the present antimicrobial drugs useless.[1-3] Antibiotic-resistant bacteria are present in two million people worldwide, causing at least 23,000 mortalities annually.[4] Antimicrobial Resistance (AMR) has emerged as one of the most important public health issues of the twenty-first century, according to the World Health Organization (WHO).[5] Furthermore, it is not surprising that a sizable fraction of people, particularly those who reside in developing countries, are using naturally accessible bioactive alternatives for their basic healthcare given the numerous drawbacks and side effects connected with current antimicrobial drugs.

More than 80% of the population in underdeveloped nations, particularly those in Africa, Asia, and Latin America, uses medicinal plants to fulfill their basic healthcare needs and wellness.[6] There are over 400,000 different plant species on the earth, and the majority of them are useful for treating a wide range of diseases. This has spurred interest in research aimed at finding "perfect" bioactive chemicals that might be helpful to humans since they have a wide range of biological features.[7-9] However, inappropriate use and over-propagation could put the plants in danger of extinction. Extensive research has demonstrated that endophytic fungus can colonize plant tissues, offer protection, and are a rich source of naturally occurring bioactive chemicals.[10]

Furthermore, the number of fungal species is thought to be 1.5 million, with a ratio of about 1:6 to vascular plants.[11] Micro-organisms known as endophytes penetrate internal plant tissues without appearing to harm the host plant at any point in their life cycle. Both parties gain from the partnership in this contact, which is referred to as a mutualistic symbiosis.[12-14] The endophytes help the plants perform their physiological and ecological functions, which results in defense and survival strategies. Additionally, endophytic fungi support growth, guard against biotic and abiotic challenges such salt, severe heat, heavy metal toxicity, and oxidative stress, as well as offer defense against insects and herbivores.[13,15,16] Endophytes can stop the

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development of resistance mechanisms by fighting off pathogenic invasion with the help of secondary metabolites.

The advantageous traits exhibited by endophytic fungus are mostly due to bioactive substances. History has demonstrated that such metabolic compounds may contribute to important discoveries, such as the discovery of penicillin, which was a turning point in the development of antibiotic drugs and was known as a "wonder drug" because it saved millions of lives.[17] Penicillin was produced by the bacterium *Penicillium chrysogenum*. Paclitaxel (Taxol), another "gold standard" bioactive substance used in chemotherapy, is produced by *Taxomyces andreanae.*[18] These bioactive metabolites can be structurally divided into a variety of groups, including alkaloids, benzopyranones, chinones, peptides, phenols, quinones, flavonoids, steroids, terpenoids, tetralones, and xanthones.[19] Numerous biological qualities, such as antibacterial, antifungal, immunosuppressant, antiviral, antiparasitic, antioxidant, anti-inflammatory, and anticancer capabilities, have been demonstrated by them.[20]

Work on interactions with host plants, ultra-structural and colonization investigations, the characterization of new metabolites, and other emerging issues connected to endophytic symbioses has rapidly increased along with the expansion in research on endophyte variety. This body of study has emphasized the differences between the unique *Clavicipitaceous* endophytes of grasses and the endophytes associated with the foliage of most plants in terms of taxonomy, ecology, and diversity.[21] Together, these studies have revealed the frequency of horizontal transmission,[22] the timescales underlying new leaf colonization,[23] the phylogenetic relationships of endophytes,[24] and their sensitivity to environmental changes,[25] their biochemical variety,[26] and the heretofore unknown unrecognized ways in which they affect the ecological phenotypes of the plants they inhabit.

The intricacy of these interactions is striking: following inoculation, plants often do not exhibit any noticeable changes in growth rate, biomass accumulation, root: shoot ratio, or other parameters that can be measured.[27] However, the significance of endophytes is made obvious when biotic or abiotic stresses pose a threat to plants. Together, these investigations just scratch the surface of the enormous iceberg that is plant-endophyte symbioses; only a small portion of these symbioses has been examined to determine the advantages and disadvantages to hosts of hosting these fungi in their photosynthetic tissues. Understanding these costs and advantages in the context of the almost mind-boggling diversity of foliar endophytes is one of the fascinating and difficult elements of endophyte ecology. Placing these many endophytic interactions in an evolutionary and ecological context serves as a powerful tool in this attempt.[28]

The ability of symbionts to co-colonize specific hosts, their capacity for direct and indirect interactions, and their own evolutionary history, as encapsulated by the genomic architecture linked to pathogenicity or other ecological modes, have all been recognized as factors that can affect the outcomes of microbe/host interactions.[29,30] Even though recent studies have shown that there aren't many hard-and-fast rules for predicting the directionality of species interactions along the mutualistic-parasite continuum, it is now obvious that context is crucial for understanding the ecological and evolutionary significance of those interactions.[31] Understanding the evolutionary history of symbioses is crucial to putting this setting in this perspective. Through extensive evolutionary investigations of endophytes, steps in this approach are being performed.[32] But more fundamentally, we still lack a thorough understanding of the diversity of fungi capable of developing endophytic symbioses with plants in any given ecosystem. This is because endophyte diversity at the levels of genotype, species, clades, and function has not yet been thoroughly investigated.

The focus of recent biotechnological developments is on the discovery and application of novel bioactive substances obtained from endophytic fungus. Despite this, only a small part of endophytic fungi have been isolated and their biological functions have been studied. In the current review, we pay close attention to the many biological traits that endophytic fungi exhibit. We also find brand-new bioactive substances linked to the activities.[33] We also provide information on efforts to combat pathogenic bacteria with resistance. These untapped niche markets will greatly advance the medication development process. Endophytic fungi are a rich source of unique, renewable, low-toxic natural bioactive chemicals that are more effective, potent, inexpensive, safe, and less resistant than traditional antimicrobial agents. Fungi as cultivated microbes have provided many of the nature-inspired syntheses of chemically diverse drugs. Endophytic fungi bioactivities attract interest, with applications in fields as diverse as cancer and neuronal injury or degeneration, microbial and parasitic infections, and others.[34] Thus, this will help the medical and pharmaceutical businesses and lessen the heavy load on public healthcare systems.

Bioactive Compounds as Alternative Antibacterial Agents

Endophytic fungi have a wide range of biological actions, including antibacterial, antifungal, immunosuppressive, antiviral, antiparasitic, antioxidant, anti-inflammatory, and anticancer properties. Numerous bioactive substances found in endophytic fungi that may be good for human health. The classes of compounds that make up secondary metabolites derived from endophytes include steroids, xanthones, phenols, isocoumarins, perylene derivatives, quinines, furandiones, terpenoids, depsipeptides, and cytochalasins.[20] These substances have been shown to have biological activities with antibiotic, antiviral, volatile antibiotic, anticancer, antioxidant, insecticidal, antidiabetic, and endophytes have a significant impact on the physiological functions of host plants, improving their ability to withstand stress, insects, nematodes, and disease.[35]

Antibiotics have become a cornerstone of traditional medicine since the invention of penicillin, and as World War II demonstrated, they have significantly lowered the fatality rate by saving millions of lives.[36] It was the first recommended antibiotic used to treat life-threatening illnesses in the 1940s. Soon after, the emergence of antibiotic resistance and, in particular, the identification of several bacteria that are resistant to antibiotics (MAR), led to a decline in the action of antibiotics.[37] The tremendous rise in germ resistance decreases the effectiveness of current antibiotics, which has a detrimental effect on how they are used in human medicine. Numerous antibiotics have entered the market during the past century, but despite these developments, there is evidence that antibiotic resistance is growing across the board.[38] Antibiotic resistance is still one of the biggest hazards to human health, and it puts a tremendous financial strain on the healthcare system, and also according to the World Health Organization (WHO).[39]

The severity of antibiotic resistance was highlighted, as well as the significance of creative research and development methods.[40] Endophytes produce secondary chemicals as part of their defense mechanisms against pathogenic invasion, according to a number of well-established studies.[15,19,41] In relation to bioactive compounds with possible antibiotic characteristics, bioactive metabolites are low-molecular-weight, organic, natural chemicals produced by microbes that have actions at low concentrations against other micro-organisms. Endophytes are known to produce a wide variety of antibacterial chemicals, including

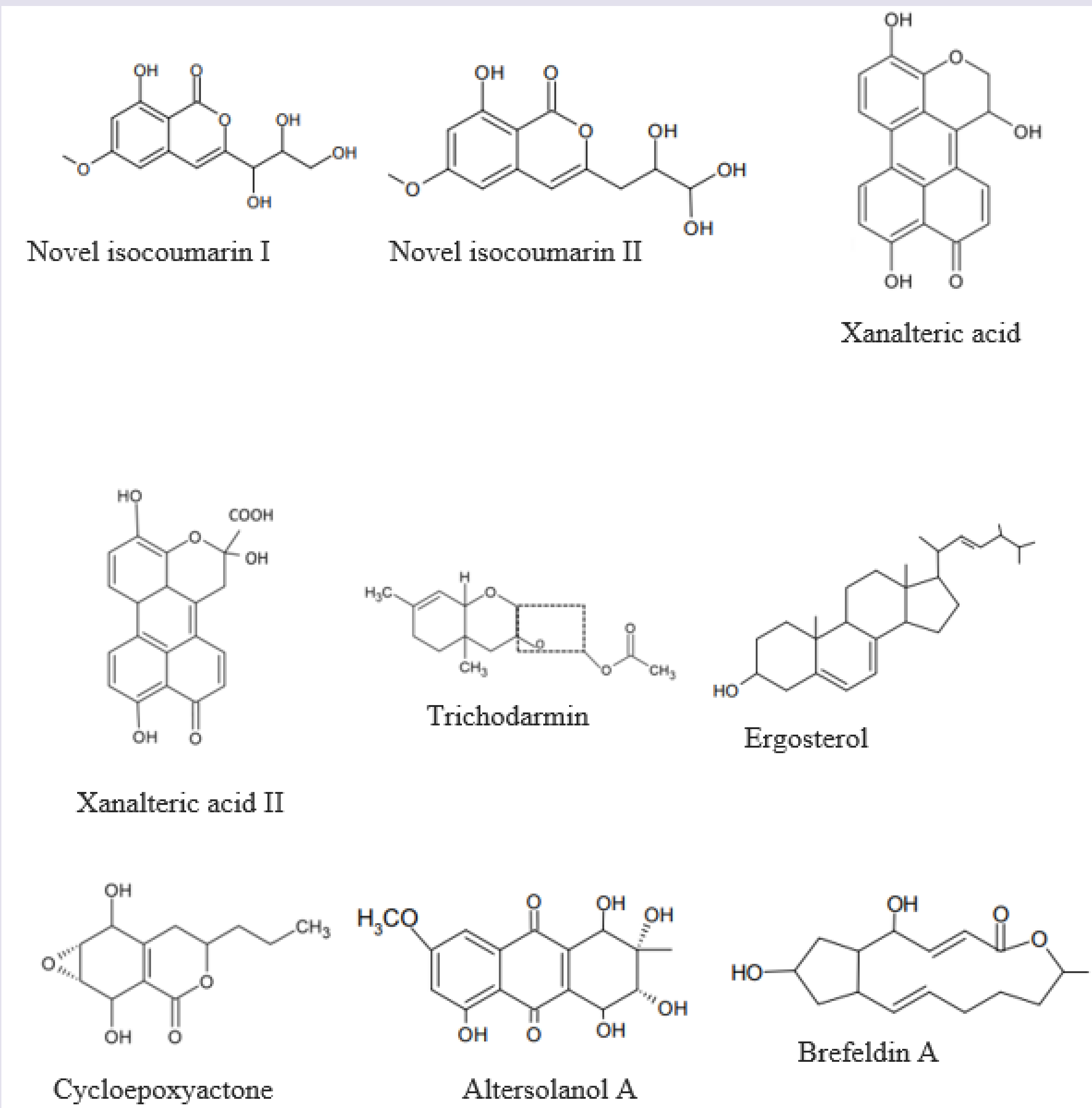

Figure 1: Chemical structures of the bioactive compounds with antibacterial activities.[49,45,56]

alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids.[33] The timeline of events in the emergence of antibiotic resistance provides us with conclusive proof of the action and the evolution of antibiotics over bacteria.[42]

With a MIC value of 62.50 mg/mL, the bioactive compounds created from endophytic fungal extracts of *Penicillium* sp. showed remarkable activity against *Enterococcus faecalis*.[43] This is the first report on the effective isolation of linoleic acid (9,12-octadecadienoic acid Z,Z) and cyclodecasiloxane generated by endophytic *Alternaria* sp. from native *Pelargonium sidoides* of South Africa. *Bacillus cereus, Escherichia coli*, and *Enterococcus faecium* were among the food-borne and food-spoiling bacteria that these fungi metabolites suppressed, while *E. gallinarum* had a 2–12 mm zone of inhibition.[33] A biocontrol investigation found that the endophytic fungus *Piriformospora indica* was able to inhibit the root-knot nematode parasite and, as a result, enhanced plant growth.[44] Root-knot nematodes, such as *Meloidogyne incognita*, are persistent parasites in plants and cause about 5% of global crop losses.

The fungus *Alternaria* sp., which was isolated from the mangrove (*Sonneratia alba*) collected in China, produced two novel secondary metabolites, 10-oxo-10H-phenaleno (1,2,3-de) chromene-2-carboxylic acids and xanalteric acids I and II.[44] *Staphylococcus epidermidis, Pseudomonas aeroginosa,* and *Enterococcus faecalis* were susceptible to the metabolites' robust antibacterial effects.[45] (Figure 1)

Using NMR and MS, a novel isocoumarin derivative with an unique butanetriol group at C-3 was found. Isocoumarin and its derivatives are widely distributed in various bioresources and have been shown to possess a series of biological activities due to the combination with different functional residues.[46] The bioactive substances also demonstrated some action against Gram-negative bacteria. With MIC values of 32 g/mL, compounds 1 and 2 were efficient against *E. coli*.[47] In addition; new ester metabolites isolated from endophytic fungi from eastern larch trees have been found in previous investigations to be effective antibacterial agents against *Vibrio salmonicida, Pseudomonas aeruginosa*, and *Staphylococcus aureus*. These substances were then identified as 8,1,5-trihydroxy-3,4,2-dihydro-1,4,2-binaphthalenyl-1,4,2-trione and the 6-oxo 2propenyl-3,6,2-dihydro-2H-pyran -3-yl ester of 2-methyloctanoic acid respectively. Antimicrobial tests and observations permitted a comparison of bioactivity potential of the activated chitosan films and the examination of the relationship between the antimicrobial properties and the mass partition coefficient.[48]

Bioactive Compounds as Alternative to Antifungal and Antibacterial Agents

The number of fungal species is currently estimated to range from 2.2 to 3.8 million in the entire planet, with soil fungal populations making up a sizable fraction.[50] This implies that there may be more fungal contact, whether advantageous or harmful. In the recent past, fungi illnesses were responsible for over 1.6 million deaths annually and over a billion people suffering from severe morbidity. Fungal infections in the agricultural industry may result in crop loss or damage, financial losses, and finally have an impact on food production and security.[51] The resistance of bacteria to modern antimicrobial treatments, particularly antifungal drugs, has also dramatically increased. There are currently few effective therapeutic options available. Despite the fact that they can infect hospitalized patients with secondary illnesses, fungi diseases are typically underappreciated and ignored. Due to their opportunistic nature and potential impact on immunocompromised persons, pathogenic fungi represent a significant burden on the world's existing healthcare systems.[52] (Figure 2)

Screening for novel bioactive compounds will help in the battle against animal and human fungal diseases is a key component of research advancements in modern antifungal drugs. With 19 and 30 mm respectively in disc diffusion assay, a novel triterpene glycoside demonstrated good antifungal inhibitory effects against *Candida* and *Aspergillus* sp. Additionally, *in vivo* research using mouse models revealed a moderate level of effectiveness against candidiasis.[53] Strobidurin G, favolon, pterulinic acid, and a 2, 3-dihydro-1-benzoxepin derivative discovered from *Favolaschia calocera* were previously unrecognized bioactive chemicals that have shown antifungal activity. Compound 1 showed Minimum Inhibitory Concentrations (MIC) of 9.37 and 18.75 μg/mL against *Candida tenuis* and *Mucor plumbeus*, respectively.[54] Similar investigations demonstrated the efficacy of endophytic fungi against *Escherichia coli, Staphylococcus aureus*, and *Vibrio alginolyticus*, with clear-zone diameters of 17.91 0.84 mm; 17.78 0.83 mm; 17.66 0.83 mm; 16.72 1.15 mm, and 13.65 0.27 mm, respectively through disc diffusion method.[55]

Pestalachlorides A ($C_{21}H_{21}C_{12}NO_5$) and B ($C_{20}H_{18}C_{12}O_5$) are chlorinated benzophenone derivatives that suppressed the growth of *Verticillium albo-atrum, Gibberellazeae*, and *Fusarium culmorum* plant pathogenic fungi, with corresponding MIC activity of 7.2, 144.4, and 114.4 mM[56] performed in antifungal bioassay by following National Center for Clinical Laboratory Standards (NCCLS) recommendations. Other well-known substances include saponin, glcopyranoside, and iridoide. By regulating plant pathogenic *Sclerotinia homoeocarpa*, endophytic *Humicola* sp. (JS-0112 strain) has proven to be an excellent option for the creation of novel fungicides.[57] Recent research has identified two novel polyketides isolated from endophytic *Phomopsis* species with an unheard-of "C_6-C_{12} carbon skeleton (CFS42). Additionally, the chemicals prevented the growth of *Curvularia lunata, Alternaria alternata, Bipolaris sorokinian*, and *Alternaria alternata*. This emphasizes the abundance of novel bioactive chemicals produced by endophytic fungi that remain and still it is not explored.[58]

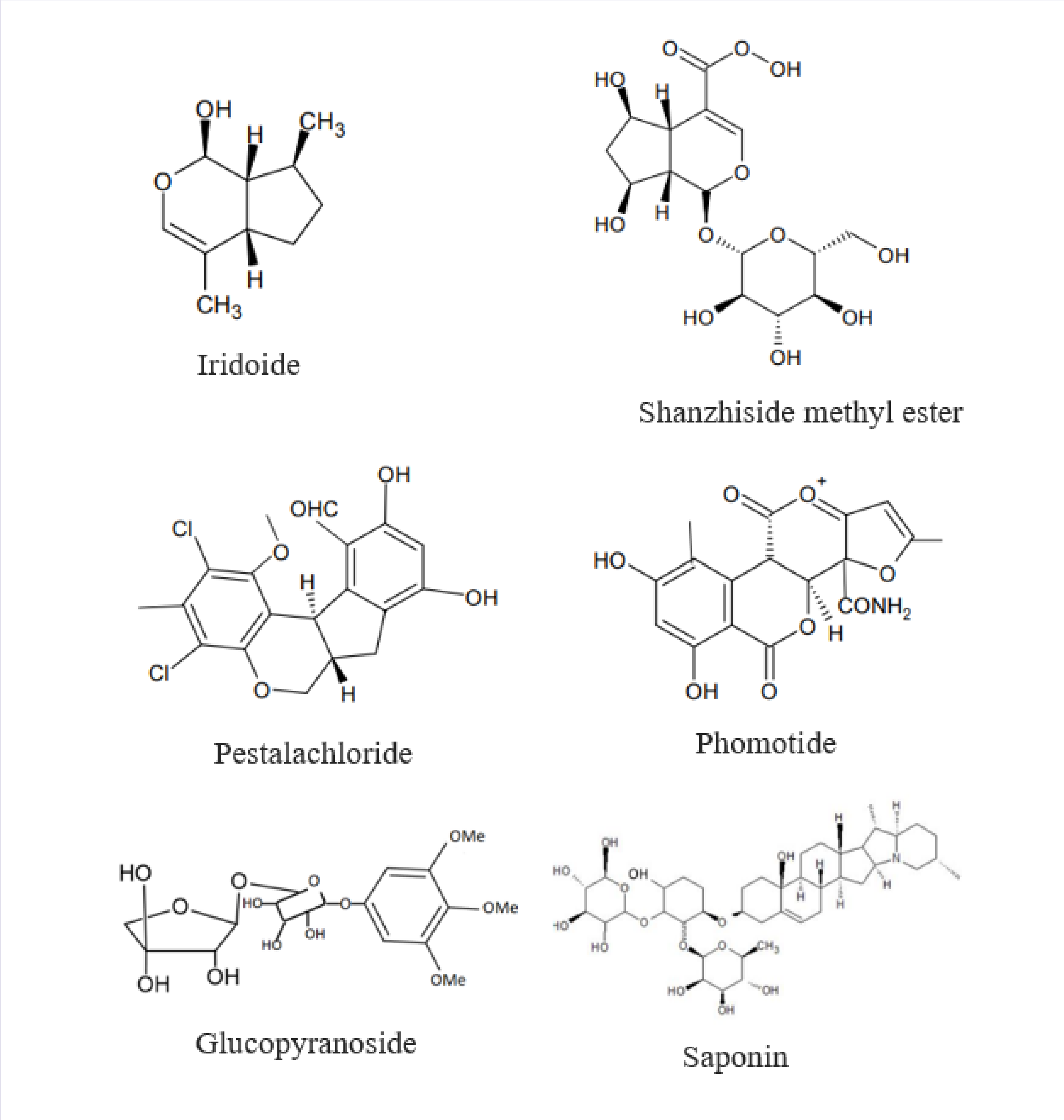

Figure 2: Chemical structures of the bioactive compounds with antifungal activities.[59]

Bioactive Compounds for Treating Cancer Cells (Anticancer Activity)

The World Health Organization (WHO) defines cancer as a class of disorders brought on by the tumor or malignant development of cells as a result of unchecked cell division.[50] One in six human deaths in 2018 were linked with cancer, which is estimated to have contributed to 9.6 million deaths globally. Cancer is the second biggest killer globally. While breast, colorectal, lung, cervical, and thyroid cancer frequently affect women, lung, prostate, stomach, and liver cancer frequently affect men. Cancer accounts for the majority (70%) of fatalities in low- and middle-income regions of Africa, Asia, Central America, and South America. Since the majority of anticancer agents are naturally lipophilic and have a high first-pass effect, therapeutic processes for treating cancer patients currently pose enormous challenges to both the doctor and the patient. These challenges stem from a lack of precision as well as a lack of bioavailability. These substances may interact with non-cancerous tissues since they are non-specific in regard to their targets. Additionally, cancer patients frequently encounter negative side effects following therapeutic procedures that are also very hazardous.[60-62] Cancers and the diseases they are connected with are thought to provide a significant healthcare burden to people around the world because of these effects.[63] This explains the motivations behind ongoing, concentrated research projects aiming at identifying novel natural bioactive substances, particularly from endophytes, that may function as substitute agents to combat cancer.[64,62]

A number of bioactive substances have anticancer properties The endophyte *Chaetomium globosum* isolated from the *Ginkgo biloba* plant contains three new chemicals, including the azaphilone alkaloids, chaetomugilides A–C, and chaetoviridin E, all of which have strong cytotoxic effects against the human cancer cell line HePG2.[63] Other endophytic fungus from the genera *Xylaria, Phoma, Hypoxylon*, and *Chalara* generate cytochalasins, which have anticancer properties. In addition, *Rhinocladiella* sp. isolated from *Tripterygium wilfordii* yielded, three novel cytochalasins:cytochalasin H, cytochalasin J, and cytochalasin E.[65] Podophyllotoxin($C_{22}H_{22}O_8$), a lignin-type bioactive compound that was first discovered in *Podophyllum peltatum L*. in the 1980s, and its derivatives are widely used as cathartic, purgative, antiviral, vesicant, antibacterial, antihelminthic, and antitumor agents due to their wide range of biological properties.[66] Chemotherapeutic drugs made from podophyllotoxin include etoposide and teniposide, which are currently used clinically to treat a variety of cancers. Additionally, endophytes belonging to the genera *Trichoderma, Penicillium*, and *Phomopsis* have been found to produce the substance podophyllotoxin, which has anticancer properties.[67]

Phenylpropanoids are a prominent class of bioactive substances that are produced naturally by plants, although several studies have revealed that endophytes also generate phenylpropanoids.[68] Phenylpropanoids block the upregulation of histone deacetylase in malignant cells, which stops the cell cycle and triggers apoptosis (Figure 3).

Phenylpropanoid derivatives with antibacterial properties can be extracted from the mangrove-associated endophytic fungus *Aspergillus* sp.[69] In another investigation, the human cancer cell lines HL-60, U937, and Jurkat were exposed to fusarubin and anhydrofusarubin, which were obtained from *Cladosporium* species. By increasing the yield of specific compounds with genetic engineering and other biotechnologies, endophytic fungi could be a promising, prolific source of anticancer drugs.[70] These compounds reduced cell proliferation and promoted apoptosis. Fusarubin dramatically decreased the percentage of cells in the S phase while increasing the percentage of cells in the G2/M phase, even though both chemicals greatly promoted apoptosis of these malignant cells with increases in concentration.[71] In contrast, anhydro fusarubin lowered the percentage of cells in the S and G2/M phases while increasing the number of cells in the G0/G1 phase.

Given the evidence that endophytic fungi have a variety of metabolites, including alkaloids, macrolides, terpenoids, flavonoids, glycosides, xanthones, isocoumarins, quinones, phenylpropanoids, aliphatic metabolites, and lactones with potent anticancer properties, there is a need to concentrate on studies that constantly assess the potential of endophytic fungi to produce bioactive compounds.[72] However, only a small portion of endophytes have been studied thus far.

Bioactive Compounds as a Potential Antioxidant Agent

Free radicals may be created through the chemical process of oxidation, which involves the loss of electrons from an atom. Free radicals are unstable molecules that are created naturally during chemical processes like digestion. These free radicals may take part in a cascade of events that may harm human cells.[74,75] This is mostly caused by the imbalance that results in cell damage when an atom loses an electron. Cells exposed to oxidative stress may experience a variety of illnesses in humans.[76] Numerous studies have shown that oxidative stress exposure causes cellular degeneration, as well as cancer, atherosclerosis, coronary heart disease, diabetes, Alzheimer's disease, hepatic and kidney damage, as well as other neurological illnesses.[77]

Novel natural bioactive chemicals protect cells from oxidative damage by preventing or lowering reactive oxygen species and free radicals. Compounds with antioxidant activity include phenolic acids, phenylpropanoids, flavonoids, lignin, melanin, and tannins.[78,79] There is strong evidence that the production of various antioxidant chemicals by endophytic fungi gives the host plants the ability to withstand some stresses. After 5 min of treatment, the endophytic fungus *Fusarium oxysporum* from the leaves of *Otoba gracilipes* demonstrated antioxidant activity, with a maximum scavenging effect of 51.5% on 2,2-diphenyl-1-picrylhydrazyl (DPPH).[80]

The medicinal plant *Ginkgo biloba* yielded a total of 41 bioactive compounds from the endophyte *Xylaria* sp., and these compounds exhibited antibacterial, antioxidant, anti-cardiovascular, and anticancer activities. Phenolic compounds including flavonoid molecules, have been demonstrated to have very potent antioxidant activities.[81] *Alternaria alternata* AE1, an endophytic fungus isolated from *Azadirachta indica*, was recently the subject of investigations that demonstrated showed it produced secondary metabolites with strong antioxidant effects.[82] The secondary metabolites demonstrated antioxidant potentials with IC_{50} values of 38.0 and 11.38 g/mL respectively in DPPH free radical and superoxide radical scavenging experiments. The residues chlorogenic acid, neochlorogenic acid, rutin, and quercetin 3-acetyl-glucoside were found in methanol extracts of two filamentous fungal strains, and the extracts significantly increased antioxidant activity.[83] Additionally, a different study discovered the biomolecules pestacin, isopestacin, and 1,3-dihydro isobenzofurans from the endophytic fungus *Pestalotiopsis microspore* housed in *Terminalia morobensis*, which

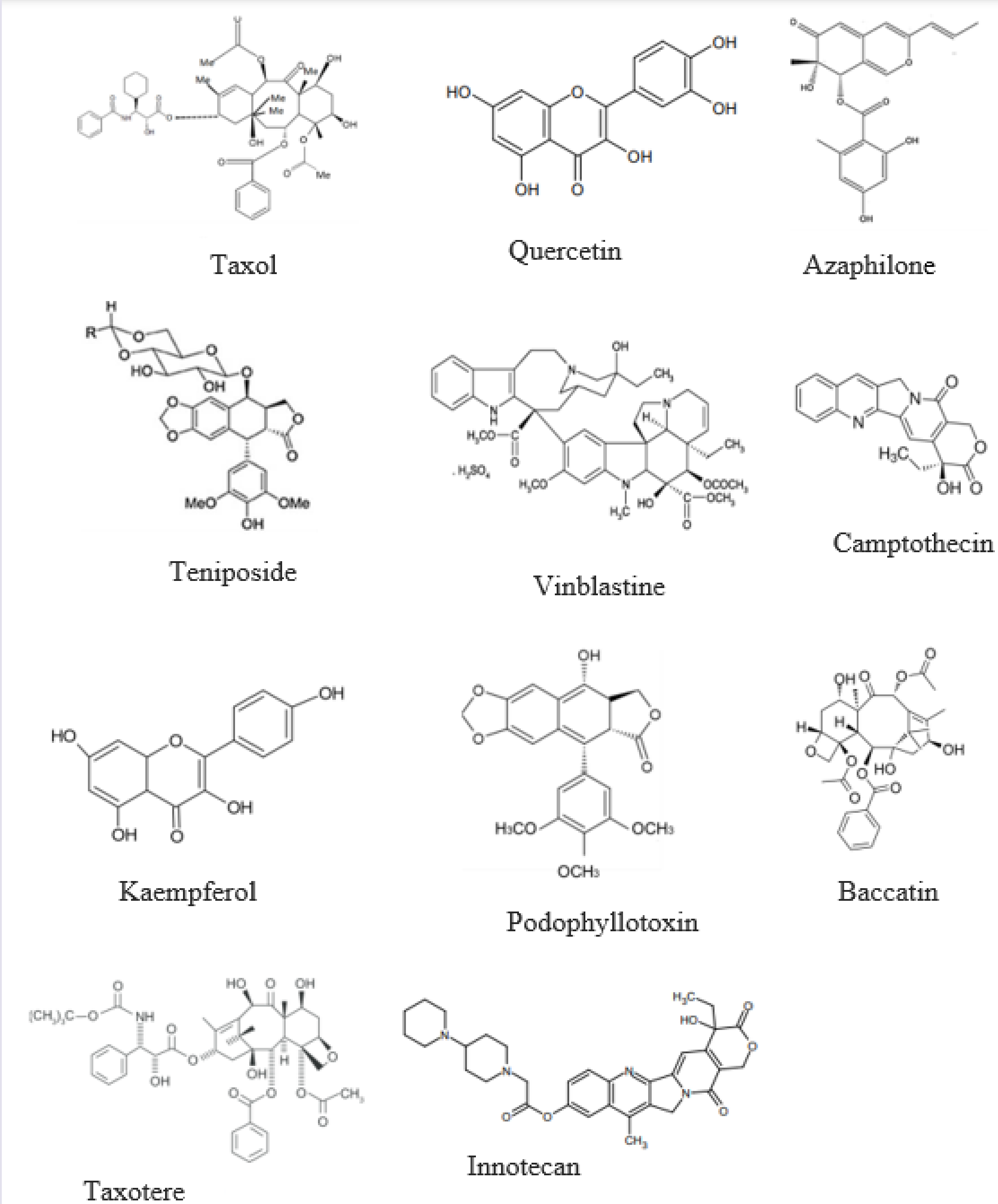

Figure 3: Chemical structures of the bioactive compounds with anticancer activities.[73,40,59]

likewise also had an highly effective antioxidant capabilities (Figure 4).

Bioactive Compounds for Treating Infectious Parasites

Protozoa, helminthes, and ectoparasites that reside on or in a host organism and depend on its resources for survival may cause parasitic infections in humans. The rate of morbidity and mortality in humans is known to be greatly influenced by disease-causing parasites, particularly in underdeveloped nations where a high proportion of the population is vulnerable.[12] Therefore, this poses serious difficulties to already overburdened public healthcare systems, leading to large financial losses. Every year, parasite-related illness is estimated at 48.4 million cases and one million fatalities. Despite this, there are now only a small number of antiparasitic medications on the market, which is particularly concerning considering the difficulties associated with parasite drug resistance.[85] Additionally, there is data that shows parasitic organisms are rapidly acquiring treatment resistance, and the resistant strains are dispersing at an alarming rate. This necessitates stepping up efforts to find new, powerful, and less hazardous chemicals that might be more effective against

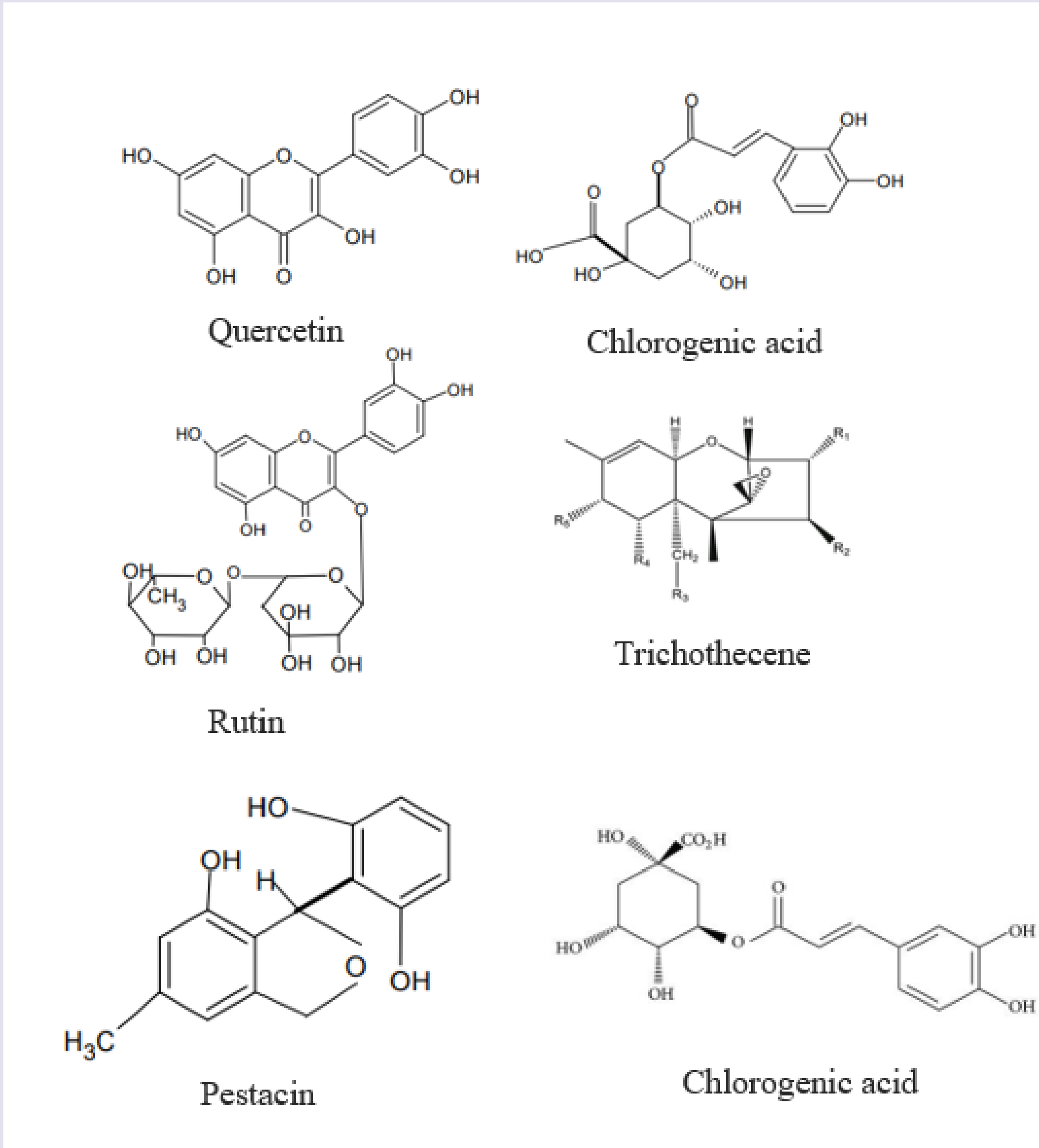

Figure 4: Chemical structures of the bioactive compounds with anticancer activities.[84]

these diseases.[86-88] There is also strong evidence that suggests endophytes produce a variety of unique bioactive substances that could be very helpful in the development of anti-parasitic medications (Figure 5).

An endophytic fungus called *Diaporthe phaseolorum*-92C (92C), which lives on the roots of the *Combretum lanceolatum*, demonstrated substantial anti-parasitic action against *Trypanosoma cruzi* by lowering the amount of amastigotes and trypomastigotes by up to 82%. With an IC_{50} of 9.2 g/mL, the bioactive compound 18-des-hydroxy cytochalasin H demonstrated nematocidal action and decreased the survival of promastigotes of *Leishmania amazonenses.*[88] Another study found that the anti-parasitic compound oxylipin(9Z,11E)-13-oxooctadeca-9,11-dienoic acid, which was derived from fungal extracts of the endophytic fungus *Penicillium herquei* strain BRS2A-AR, was effective against *Plasmodium falciparum* 3D7, *Trypanosoma brucei, Leishmania donovani* (as well as other *Leishmania* sp.), having IC_{50} values lower than 100 μM, therefore showing very excellent anti-parasitic activities.[89] Two novel alternarlactones A and B that belong to the class alternariol were generated by *Alternaria alternata* P1210 from the roots of the halophyte *Salicornia* sp. These compounds had anti-parasitic potential, although this was a preliminary study and substantially more work is required.[90]

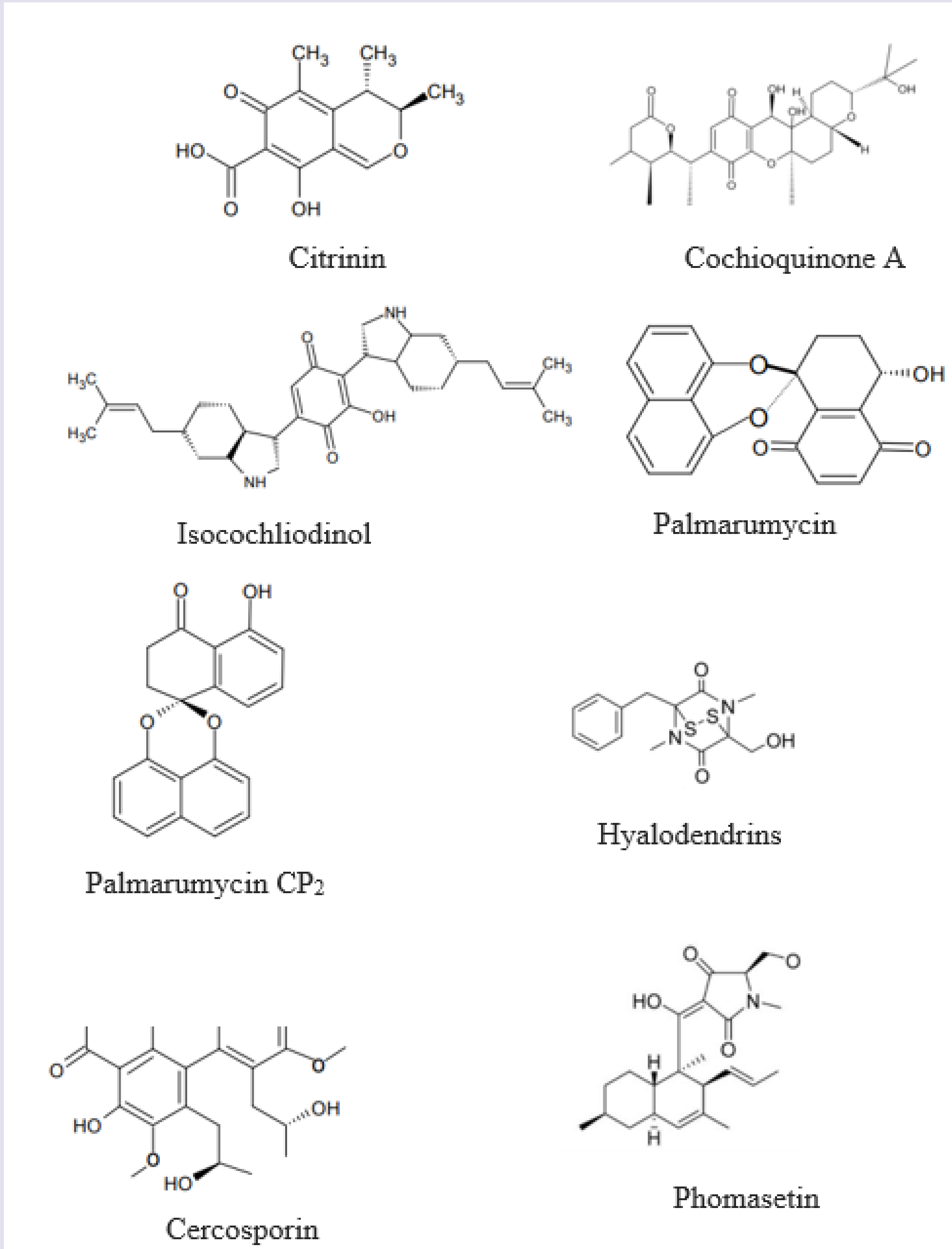

Figure 5: Chemical structures of the bioactive compounds with anticancer activities.[91]

Bioactive Compounds with the Potential of Serving as Immunosuppressive Drugs

Immunosuppressive drugs, sometimes referred to as anti-rejection drugs, are given to transplant recipients to suppress, decrease, or prevent allograft rejection.[20] They are also crucial in the management of autoimmune diseases like insulin-dependent diabetes, lupus, psoriasis, and rheumatoid arthritis.[92] There is a need to speed up the search for safer but more effective medications to address these issues as the effectiveness of immunosuppressive medications is currently impacted by a number of negative effects. Endophytes are capable of creating bioactive compounds with immunosuppressive potential, according to a number of studies.[92,93] The endophyte *Mycosphaerella nawae* ZJLQ129, isolated from Smilax china leaves, produces a novel amide derivative called mycousnine enamine. Furthermore, by preventing the production of the surface activation antigens CD25 and CD69, cyclosporin A and (-) mycousnine enamine have preferentially reduced T cell proliferation.[94] These results support the possibility that powerful immune suppressants with low toxicity but high selectivity may be derived from endophytic fungus (Figure 6).

In addition to these, a total of nine polyketides were isolated from the endophytic fungus *Penicillium* sp. ZJ-SY2, which was connected to the leaves of the mangrove *Sonneratia apetala*. These polyketides included two novel benzophenone derivatives, peniphenone and methyl peniphenone, and seven well-known xanthones (Figure 7). With IC_{50} values ranging from 5.9 to 9.3 μg/Ml,[95] these substances demonstrated good immunosuppressive effects. Eighteen novel nor-isopimaranediterpenes, referred to as xylarinorditerpenes A-R (1-18), including those with immunosuppressive potential, were isolated from *Xylaria longipes* HFG1018, a basidiomycete that is connected to wood rot.[94]

Bioactive Compounds with Antiviral Properties

One of the main causes of mortality and illness in humans worldwide is viruses, which are micro-organisms that only replicate within living cells. The use of modern antiviral medications and vaccinations is essential in the fight against human life-threatening diseases.[97] Additionally, the development of viral medication resistance diminishes the therapeutic efficacy of the existing antiviral treatments, raising serious concerns for global public health. Effectively, ideal antiviral medications should be effective against the desired virus strains while having little negative effects on the host cells. Antiviral medications' modes of action are typically aimed at preventing or suppressing infection by targeting viral proteins or the host cellular components that viruses rely on to replicate and establish control over cellular processes.[98,99] It is essential to look for, discover, and develop novel, affordable, and more effective antiviral medications as well as vaccines to address this issue. Research has been done to determine whether endophytes have the potential to produce promising natural bioactive substances with antiviral activities.

The endophytic fungus *Emericella* sp. (HK-ZJ) from the mangrove plant *Aegiceras corniculatum* produced several isoindolone compounds, including emerimidines A and B, emeriphenolicins A and D, aspernidines A and B, austin, austinol, dehydroaustin, and acetoxydehydroaustin. The cytopathic effect (CPE) test in a bioassay demonstrated the effectiveness of the fungal extracts against the H1N1 influenza A virus.[100] Herpes simplex virus was susceptible to some of the antiviral effects of fungi extracts from *Nigrospora sphaerica* (No. 83-1-1-2), *Alternaria alternata* (No. 58-8-4-1), and *Phialophora* sp. (No. 96-1-8-1). (HSV). The extraction and identification of chemicals showed two novel heptaketides, (+)-2S,3S,4aS)-altenuene(1a) and (2S,3S,4aR)-isoaltenuene, as well as six recognized compounds, including alternariol4), alternariol-9-methyl ether, and 4-hydroxyalternariol-9-methyl ether.[101] Figure 7.

Endophytic fungi with notable antiviral activities against the Herpes Simplex (HSV-2) and Vesicular Stomatitis Viruses (VSV) were recently discovered from medicinal plants of Egyptian origin.[102] The endophyte *Pleospora tarda* was found to be the source of the effective antiviral chemicals known as alternariol and alternariol-(9)-methyl compounds. A new, extremely rare 14-nordrimane sesquiterpenoid was discovered by Lui *et al*. (2019) in the endophyte *Phoma* sp., which was isolated from the roots of *Aconitum vilmorinianum*.[103] The A/Puerto

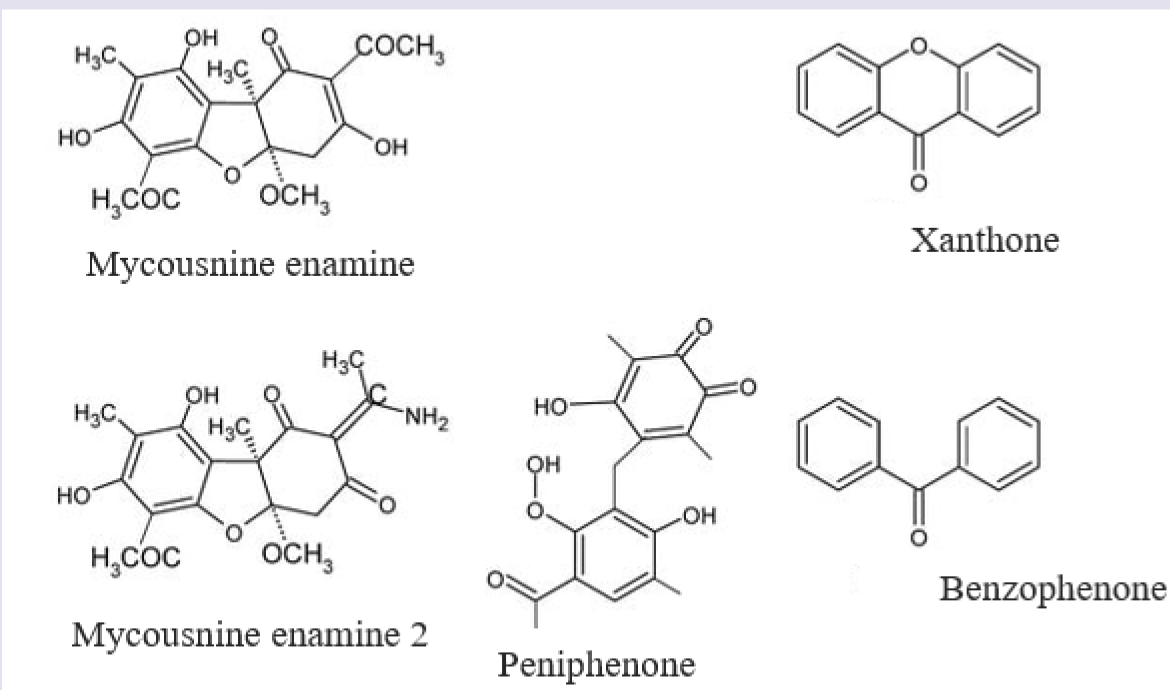

Figure 6: Chemical structures of the bioactive compounds with immunosuppressive activities.[96]

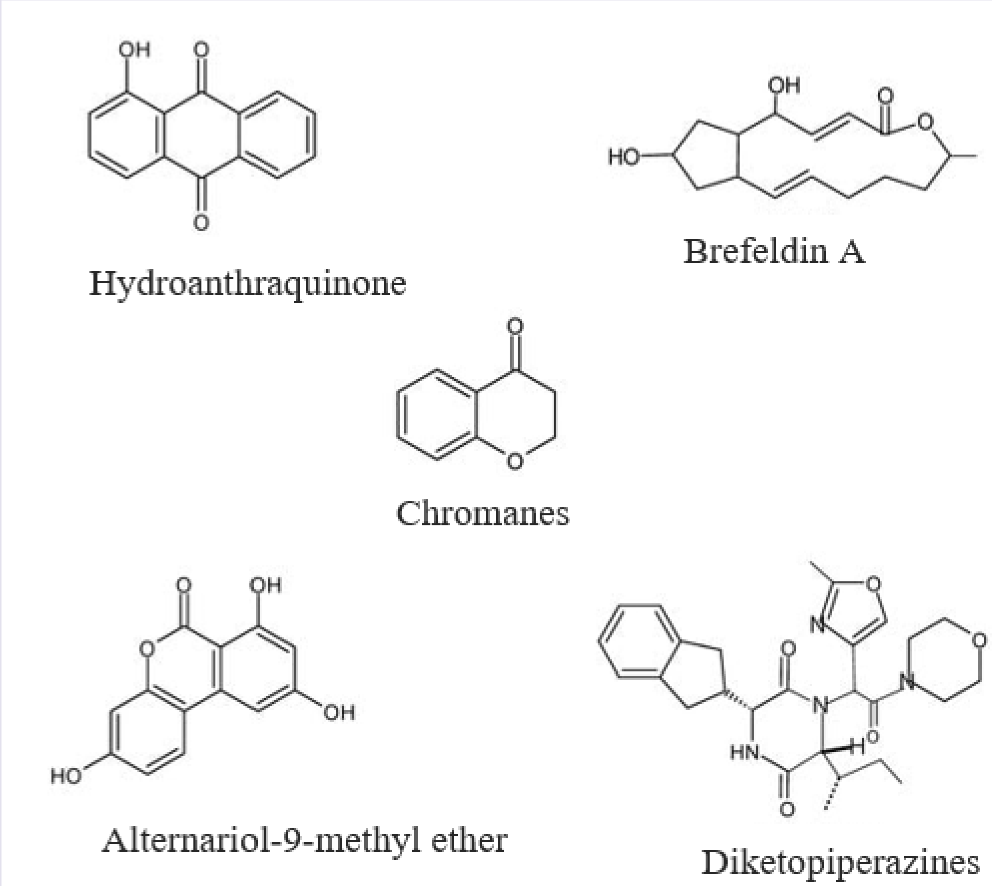

Figure 7: Chemical structures of the bioactive compounds with antiviral activities.[12,20,40]

Rico/8/34, H1N1 influenza A virus was likewise slowed down by the chemicals. The bioactive substances 6-methoxymellein, 7-hydroxy-3, 5-dimethyl-isochromen-1-one, norlichexanthone, 6-methylsalicylic acid, and gentisyl alcohol also have antifungal properties. In addition, azaphilones, 8,11-didehydrochermesinone B, and (7S)-7-hydroxy-3,7-dimethyl-isochromene-6,8-dione have recently been identified as substances from the culture extract of *Nigrospora* sp. YE3033, which is found in the plant *Aconitum carmichaeli*. These substances demonstrated potent antiviral activity against the influenza virus strain A/Puerto Rico/8/34 (H1N1).[104]

CONCLUSION

Endophytes offer a good substitute for drugs that are becoming increasingly ineffective against a variety of diseases since they are a storehouse of unique bioactive substances with a wide range of biological activities. Due to their wide distribution and easy accessibility, endophytic fungi have garnered a lot of attention in the drug development process during the past several years. Numerous studies have reported the successful isolation of novel, beneficial bioactive compounds from endophytic fungi that exhibit biological properties such as antibacterial, antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, insecticidal, immunomodulatory, antiviral, anticancer activities, etc. Despite this, only a small amount of research has been done on the useful bioactive substances produced by endophytic fungi. To speed up the screening of new biomolecules for the treatment of several life-threatening diseases and protect human health, research priority must shift toward biotechnological developments. Endophytes contain an undiscovered richness of unique bioactive chemicals, ensuring the identification of new bioactive substances for possible uses in the food, medicine, agricultural, and pharmaceutical industries.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AMR: Antimicrobial Resistance; **WHO:** World Health Organization; **MAR:** Multiple Antibiotic Resistance; **NMR:** Nuclear magnetic resonance; **MS:** Mass spectrometry;

MIC: https://en.wikipedia.org/wiki/Minimum_inhibitory_concentrationMinimum inhibitory concentration; **g/mL:** Grams per milliliter; **mm:** Millimetre; **NCCLS:** National Center for Clinical Laboratory Standards; **CFS:** Carbon Fiber Skeleton; **DPPH-α:** α-diphenyl-β-picrylhydrazyl; **IC_{50}:** Inhibition Concentration; **CPE:** Cytopathic effect; **H1N1:** h(aemagglutinin type)1 and n(euraminidase type) 1; **Sp:** Species.

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