IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
February 2024 Vol.:30, Issue:2

Utility Potentials of Fungal Extract Products as Benign Drug Principles

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Obinna Ofoegbu, Onche Emmanuel, Ajakaye Oluwadolapo Joy, Lullah-Deh Japheth A., Itodo Anthony

Polymer, Nano and Molecular Recognition Materials Research Group, Department of Industrial Chemistry, College of Physical Sciences, Joseph Sarwuan Tarka University, Makurdi, Benue State.

Submitted: 25 January 2024
Accepted: 31 January 2024
Published: 29 February 2024

ijppr.humanjournals.com

Keywords: Fungal extract, Antibiotic, Antimicrobial, Antibacterial, Anti-fungal

ABSTRACT

Fungi, which are diverse microorganisms, have gained attention for their potential use in developing safe and effective drugs. This review examines the different applications and therapeutic benefits of fungal extracts in the pharmaceutical industry. Fungal metabolites, which are bioactive and have a diverse structure, offer many promising drug development and discovery opportunities. The review provides an in-depth analysis of various fungal species and their bioactive compounds, highlighting their pharmacological properties and mechanisms of action. Additionally, the ecological significance of these fungal products is considered, emphasizing sustainable practices in drug development. The review critically assesses recent research findings and clinical trials, providing insight into fungal-derived drugs' efficacy and safety profiles. The potential challenges and future directions of harnessing fungal extracts as safe and effective drugs are also discussed. In summary, this comprehensive review consolidates current knowledge on the potential benefits of fungal extract products in drug development. The exploration of fungal metabolites as sources of novel therapeutic agents shows promise for advancing pharmaceutical science toward more sustainable and eco-friendly practices.

1 INTRODUCTION

Antibiotics are vital in fighting bacterial infections and have considerably improved the quality of human life since their introduction. However, in recent decades, this progress has been threatened as many commonly used antibiotics have become less effective against certain illnesses. This is not only because many antibiotics can produce toxic reactions but also due to the emergence of drug-resistant bacteria. Consequently, the health benefits of antibiotics are at risk, and it is crucial to find new ways to combat bacterial infections. It is essential to combat drug resistance among microorganisms. This requires searching for new compounds. Fungi are capable of producing a diverse range of secondary metabolites that exhibit fungistatic or bacteriostatic activity. Hence, they are a promising source of these compounds. These metabolites can be used as an alternative to traditional antibiotics. Additionally, fungi can accumulate compounds that possess antiviral properties [130].

Fungi produce diverse low molecular weight secondary metabolites (SMs) with varied biological activities [59; 66]. Fungal metabolites have brought about a revolution in the biotechnology industry due to their remarkable properties. Penicillin, a β-lactam antibiotic, and lovastatin, a cholesterol-lowering drug, are two excellent examples of such metabolites. The discovery and application of these metabolites have opened up new avenues for developing innovative solutions to combat diseases and enhance human health. The biogenetic compounds of fungi can be divided into primary and secondary metabolites [62]. Primary metabolites are compounds derived from the primary metabolism of sugars (monosaccharides, disaccharides, polysaccharides, sugar alcohols, and quaternary amine bases). Secondary metabolites are compounds that can be further subdivided into compounds derived from the metabolism of active acetate (polyketides, isoprenoids, and sterols); compounds derived from the metabolism of fatty acids (polyacetylenes); compounds derived biogenetically from shikimic acid (phenols and phenolic acids); compounds formed from the transformation of amino acids (amines, toxic amines, alkaloids, and peptides); and compounds formed from the transformation of aromatic amino acids (ergot alkaloids) [62]. Fungal metabolites can be divided into two categories - nitrogenous and non-nitrogenous compounds. Nitrogenous compounds include urea, amino acids, peptides, proteins, lectins, amines, alkaloids, indole derivatives, vitamins, purine compounds, isoxazole derivatives, and phenoxazine derivatives. On the other hand, non-nitrogenous compounds include

carbohydrates, lipids, polyacetylenes, polyketides, isoprenoids, sterols, organic acids, and phenolic compounds [20].

The rising rate of bacterial resistance to antibiotics is becoming a serious concern in the clinical and agriculture fields. As a result, scientists are exploring other microbial sources that can combat these resistant bacteria. Developing feasible alternatives to antibiotics is crucial to protect and promote global public health [39; 18; 17; 31; 99].

Finally and most importantly, the high level of antibiotic resistance poses a significant threat to humanity. With the current crisis in both the European Union and South America, there will be reduced funds available for research and healthcare. This could lead to a faster and easier spread of antibiotic-resistant bacterial strains in both the community and hospitals [80]. Developing new treatments and preventive measures for infectious diseases, such as vaccines and probiotics, can be a challenging and expensive process. Only a very small percentage of new molecules tested -- about 5 out of 260,000-530,000 -- show antimicrobial activity each year. Additionally, these molecules often have high production costs, are highly toxic, and require complex synthesis [98].

This review article aims to explore the potential benefits of using fungal extracts as a safe drug source, highlighting recent advancements in the field. Both the development of fungal extracts and metabolites are covered in this review, along with the diverse range of antimicrobial, antibacterial, antifungal, and antiviral compounds produced by various fungi. The paper also describes the properties of chemical compounds extracted from fungi that have applications in pharmaceuticals, specifically their antimicrobial activity. The main objective of this review is to answer the question of how fungi can be used as a source of antimicrobial compounds to combat drug resistance in microorganisms and what their potential applications are, including their use in pharmaceuticals.

2.0 Utility Potentials of Fungal Extract

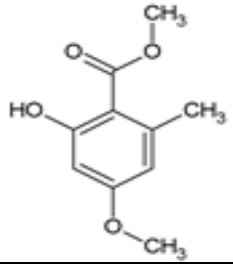
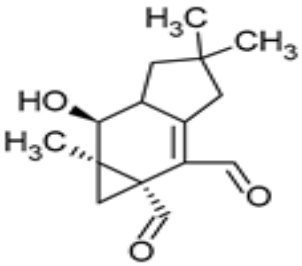
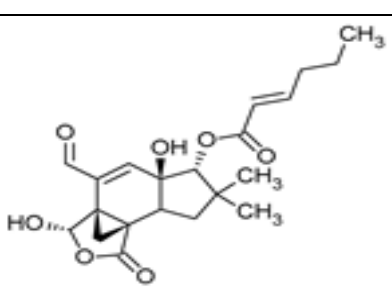
2.1 Antibacterial Properties and Compounds of Fungal Origin with Antibacterial Activity

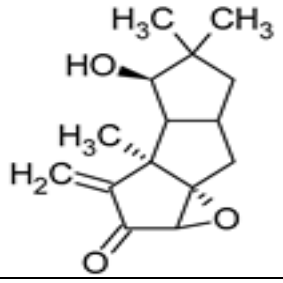
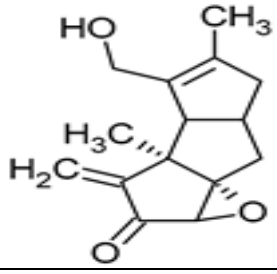
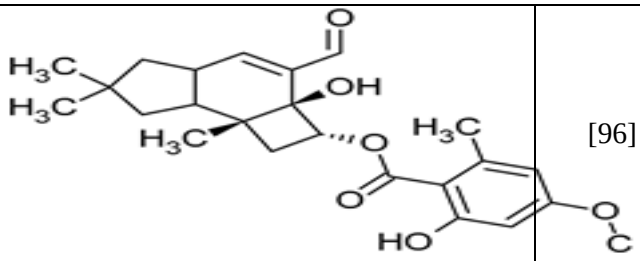
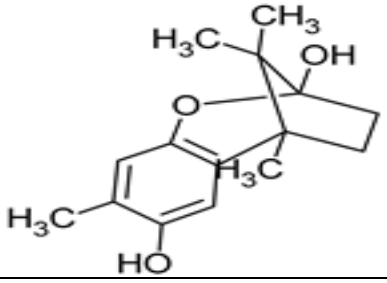
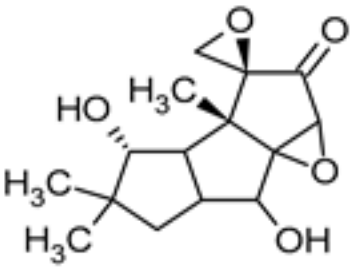
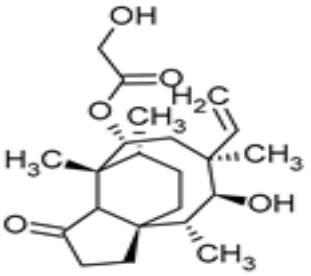
Natural products are a plentiful source of antimicrobials [138]. In the kingdom of fungi, extensive biosynthetic capabilities are leading to the production of compounds with complex chemical structures that exhibit high biological activity. Operating as saprophytic organisms,

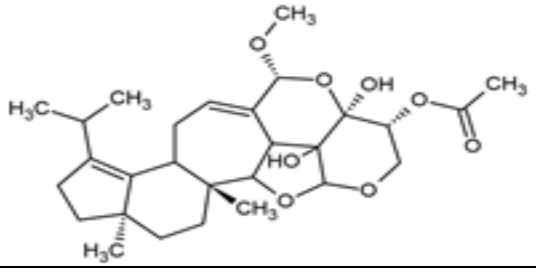
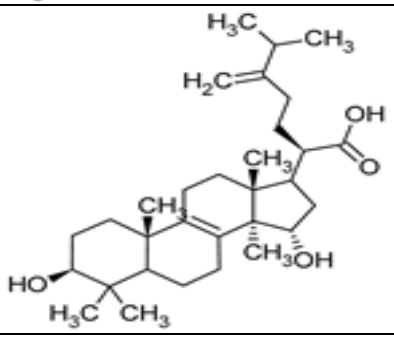
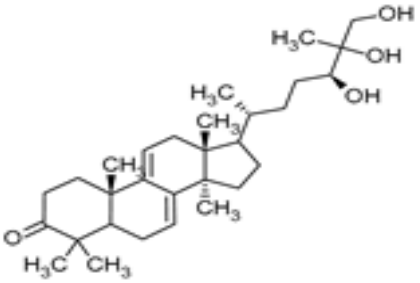
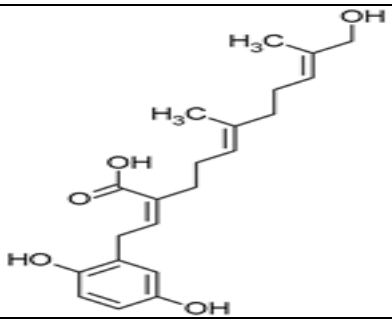
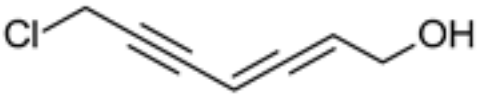
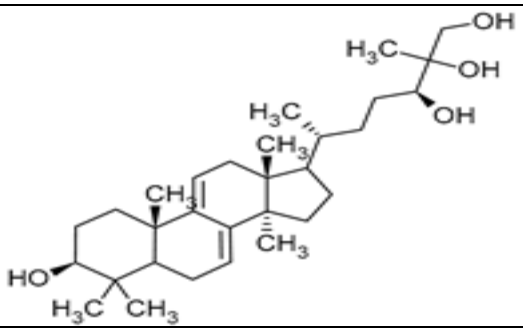
fungi are strongly biochemically related to the composition of the substrate on which they reside [130].

Numerous scientific studies indicate the antimicrobial activity of individual compounds and specific extracts obtained from fungal fruiting bodies. It is believed that the presence of fungal fruiting bodies with such properties is due to defense mechanisms formed by fungi to survive in the environment. As the challenge of bacterial resistance to existing antibiotics grows, a variety of naturally occurring compounds exhibiting antimicrobial activity against pathogenic organisms is garnering increasing attention. Notably, one of the first compounds with antibacterial activity was the antibiotic substance sparassol, which was isolated from Sparassis crispa in 1920 [122] (Table 1). Over the following decades, the antibiotic activity of more than 2000 macromycetes species was subsequently validated.

Table 1. Examples of Chemical structures compounds with the antibacterial activity of fungal origin.

Group of Compounds	Compound	Species	Chemical Formula	Reference
Benzoic acid derivative	Sparassol	Sparassis crispa		[22]
Sesquiterpenes (C15)	Merulidial	Merulius tremendous		[108]
	Pilatin	Flagelloscypha pilatii		[45]

	Hypnophilin	Pleurotellus hypnophilus		[65]
	Pleurotellol	Pleurotellus hypnophilus		[65]
	Armillaria acid	Armillaria mellea		[96]
	Enokipodin A	Flammulina velutipes		[131]
	Coriolin	Coriolus consorts		[20]
Diterpenes (C20)	Pleuromutilin	Clitopilus passeckerianus		[95]

	Striatin A	Cyathus striatus		[47]
Triterpenes (C30)	Sulphuric acid	Laetiporus sulphureus		[125]
	Ganodermanontriol	Ganoderma lucidum		[77]
Meroterpenoids (C40)	Ganomycin A	Ganoderma Pfeifer		[85]
Acetylene derivatives	Scorodonin	Marasmius scorodonius		[7]
Sterols	Ganoderiol	Ganoderma lucidum		[77]

2.2 Antibacterial Compounds of Fungal Origin

Fungi are known for producing a wide variety of compounds endowed with antibacterial activity [1]. Antibiotics are substances that inhibit the growth and division of bacteria. They

exhibit a dual nature, providing a broad spectrum of activity while also showing selective efficacy against specific bacterial strains. The term "antibiotic" was coined by microbiologist Selman Waksman, who discovered two antibiotics: streptomycin and neomycin [22]. Nowadays, antibiotics come in various forms, including natural substances, semisynthetic derivatives, and synthetic analogs. These agents selectively target different bacterial structures, resulting in either a bactericidal or bacteriostatic effect. Antibiotics are grouped based on factors such as their method of action, chemical structure, or activity spectrum. For example, certain antibiotics hinder the production of bacterial cell walls (e.g., β-lactams), while others obstruct protein synthesis (e.g., chloramphenicol, tetracycline) or interfere with bacterial RNA and DNA nucleic acids (e.g., quinolones) [51]. In the early 20th century, small doses of penicillin proved highly effective in controlling a significant proportion of bacterial infections. However, as the use of penicillin increased, so did the prevalence of antibiotic-resistant bacteria [29]. Filamentous fungi, including Penicillium, Cephalosporium, Aspergillus, and Fusidium play a crucial role in pharmaceutical biotechnology, particularly in the pharmaceutical industry. These fungi are well-known for being efficient producers of antibiotics. Along with actinomycetes, they are recognized as the primary sources of antibiotics [24]. Penicillins, cephalosporins, fusidans, fusafungin, and fumigation (helvolic acid) are among the most significant classes of antibiotics produced by fungi.

2.2.1 Penicillin

Penicillins belong to the β-lactam group of antibiotics (Figure 1). Penicillins and other β-lactam antibiotics have a thiazolidine ring conjugated with a β-lactam ring in their chemical structure. Their mechanism of action involves binding to penicillin-binding proteins (PBPs) and blocking their function. These antibiotics have minimal toxicity against human cells because they only affect cells involved in peptidoglycan synthesis. Thus, they are safe to use and have low levels of general and organ toxicity. The commercial production of penicillins involves selected species such as Penicillium chrysogenum, Penicillium baculatum, Penicillium turbatum, Aspergillus persicinum, Aspergillus flavus, Aspergillus giganteus, Aspergillus nidulans, Aspergillus oryzae, and Aspergillus parasiticus [15; 82]. Penicillins are antibiotics commonly used to treat bacterial infections, such as impetigo, erysipelas, and acne, and can contribute to wound healing [82].

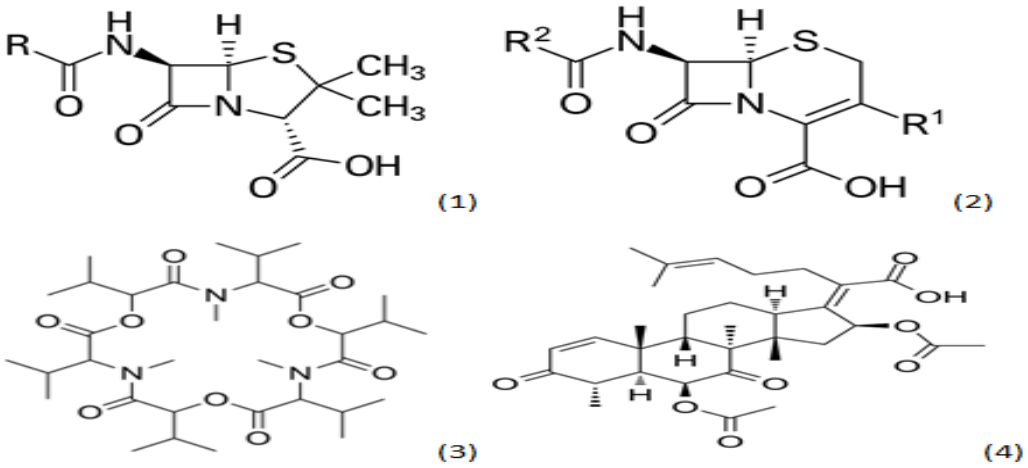


Figure 1. Chemical structures of 1. Penicillin; 2. Cephalosporin; 3. Fusafungine; and 4. helvolic acid.

Image Source: Wikipedia, Retrieval Date: 28th Jan, 2024.

2.2.2 Cephalosporin

The fungi Cephalosporium acremonium yielded cephalosporins, first isolated by Giuseppe Brotzu in 1948 [13; 35] (Figure 1). The mechanism of action of cephalosporins is similar to that of β-lactam antibiotics. These compounds are commercially produced by strains of C. acremonium and Paecilomyces pernicious. Cephalosporins can be divided into several subgroups based on their chemical structure (P1–P5) [35]. Cephalosporins, like all β-lactam antibiotics, work by inhibiting the formation of bonds that connect the subunits of peptidoglycan (murein), thus preventing the formation of a complete cell wall. They form covalent attachments to the active centers of bacterial enzymes, carboxypeptidase, and transpeptidase, leading to the inhibition of their actions. Consequently, they prevent the synthesis of bacterial cell walls. Cephalosporins are used to treat bacterial infections caused by various types of bacteria including both Gram-positive and Gram-negative bacteria. They are effective in treating infections caused by pathogens such as Staphylococcus aureus and Escherichia coli, among others [60]. Cephalosporins are effective in treating skin diseases caused by microorganisms. They have been commonly used in dermatology to address conditions such as folliculitis and postoperative infections [43].

2.2.3 Fusidans

Fusidic acid is one of the most well-known fusidans. It can inhibit the protein synthesis of Gram-positive bacteria. The compound was first isolated in 1962 from Fusidium coccineum and later extracted from Mucor ramannianus and Isaria kogana [25; 118]. Biotechnological methods are used to extract fusafungin from species such as Calcarisporium arbuscula, Fusidium coccophilum, and Mortierella ramanniana [25]. Fusidic acid is an antibiotic that can inhibit the growth and multiplication of bacterial cells. It works by preventing the synthesis of bacterial proteins. Fusidic acid is effective against a narrow range of bacteria, specifically Gram-positive bacteria, particularly those that are resistant to penicillin, like Staphylococcus strains. However, the use of fusidic acid during treatment may lead to the emergence of resistant Staphylococcus strains. This antibiotic is available in the form of creams and ointments for the topical treatment of infections such as impetigo, boils, inflammation of sweat glands and hair follicles, atrophy, acne vulgaris, and infections caused by the genus Staphylococcus spp [118; 72]. Fusidic acid is noteworthy in its ability to permeate the skin barrier, with its penetration influenced by factors such as the duration of antibiotic exposure and the condition of the skin. The biological half-life of fusidic acid is approximately 4-5 hours. Once absorbed into the bloodstream, fusidic acid undergoes significant metabolism in the liver. Although it is primarily excreted through the bile, a small portion is eliminated unchanged in the urine [34]. Although not typically used in cosmetics due to their medical nature, these compounds are effective against skin disease-causing pathogens such as S. aureus and Staphylococcus epidermidis [118].

Fusafungine is a type of peptide antibiotic that can prevent the growth of many harmful microorganisms (as shown in Figure 1). Apart from its antibacterial properties, it is also known for its anti-inflammatory effects. This is because it can activate NK cells, stimulate lymphocytes to produce IL-2 and inhibit proinflammatory cytokines [68]. Fusafungine is an effective treatment for pharyngitis that offers an alternative to systemic antibiotics, steroids, or anti-inflammatory drugs. It is sourced from the entomopathogenic fungus Fusarium lateritium (Ascomycota) and has an expansive activity spectrum without inducing bacterial resistance. As an ionophore antibiotic, it contains enniatins and has a unique ability to form complexes with potassium cations, which it transports across the lipid membranes of liposomes selectively. The topical application of fusafungine has been utilized, while its aerosol form has shown promise in treating inflammation of the upper and lower respiratory

tract. Clinical trials have confirmed the effectiveness of the aerosolized form of this medication [74].

Fumigacin and phenolic acid (Figure 1) are antibiotics and phytotoxic substances produced by fungi of the Ascomycota category. These fungi include Aspergillus fumigatus, Cephalosporium caeruleus, and Sarocladium oryzae, which are known as plant pathogens, as well as Emericellopsis terricola. Fumigacin has unique properties and a wide range of effects, making it similar to cephalosporins, particularly those in the P1 group [134].

2.3 Selected Compounds of Fungal Origin from the Group of Isoprenoids, Peptides, and Acetylene Derivatives

Compounds with antibiotic properties found in macrofungi include isoprenoids, peptides, nucleosides, and acetylene derivatives.

2.3.1 Isoprenoids

Isoprenoid compounds are a group of diverse secondary metabolites that are found in Basidiomycota. These compounds are closely linked to the biogenetic pathway that originates from active acetate and proceeds through mevalonic acid, ultimately leading to the formation of "active isoprene". Further transformations of active isoprene undergo a series of changes, resulting in the production of different compounds, including monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and steroids {114; 93].

Merulius tremendous liquid cultures produce Merulidial, containing an unsaturated dialdehyde functional group (Table 1). This compound shows potent activity against a range of Gram-positive bacteria, including Micrococcus roseus, Corynebacterium insidiosum, Bacillus brevis, Bacillus subtilis, Streptomyces viridochrontogenes, Sarcina lutea, and Arthrobacter citreus, as well as Gram-negative bacteria like Proteus vulgaris [6]. Pilatin, a derivative of marasman (Table 1), is extracted from Flagelloscypha pilati. It is effective against Gram-negative bacteria, including Salmonella typhimurium, at concentrations ranging from 5 to 50 µg/mL [45]. Three metabolites with antibiotic activity have been identified from mycelial cultures of Pleurotellus hypnophilus. These metabolites include hypnophilin, pleurotellol, and pleurotellic acid, all of which are sesquiterpenes derived from hirsutane. The common structural feature shared by all three metabolites is the α-methylenketone moiety. Hypnophilin has been extensively studied for its antimicrobial and antioxidant properties,

making it an interesting compound for further investigation. Its potential use in skincare and cosmetics is mainly due to its antioxidant activity, which can help protect the skin from oxidative stress and promote overall skin health. Pleurotellol, on the other hand, has been found to possess antibacterial and antifungal properties, making it a promising candidate for formulations targeting skin conditions caused by microbial overgrowth. Therefore, both hydrophilic and pleurotellol have potential applications in the cosmetic and skincare industry due to their beneficial properties [79]. Lentinellic acid is a type of iludane sesquiterpene (Table 1) that displays potent antibacterial properties. It has been extracted from two species of the Lentinellus genus, namely Lentinellus omphalodes and Lentinellus ursinus. This compound is effective against Gram-positive bacteria such as B. brevis, Aerobacter aerogenes, and C. insidiosum, exhibiting activity at concentrations ranging from 1 to 5 µL/mL [127]. Sesquiterpenoids are compounds with antimicrobial properties that can potentially aid in the development of new skincare and cosmetic formulas that target skin-related issues caused by microorganisms. Moreover, their potential antioxidant and anti-inflammatory activities may further augment their suitability for cosmetic applications, promoting skin health and overall product quality. It's worth noting that Lentinellic acid methyl ester has antifungal properties [127]. In the context of skincare and cosmetics, this compound may have potential applications as a preservative in cosmetic formulations to help solve skin problems caused by fungal infections such as athlete's foot or fungal acne Cadeli Sulphurenic acid (Table 1), and eburicoic acid are triterpenes isolated from Laetiporus sulphureus [125]. Pleuromutilin, a diterpene compound, was isolated by Kavanagh in 1951 from a saprophytic fungus Clitopilus passeckerianus (formerly Pleurotus passeckerianus) (Table 1). Pleuromutilin and its derivatives inhibit bacterial protein synthesis by binding to the peptidyltransferase component of the 50S subunit of ribosomes Novak and Shlaes (2011). Striations A, B, and C are kyatan diterpenes isolated from Cyathus striatus (Table 1). These compounds exhibit antibiotic and cytotoxic effects at concentrations of 2 µg/mL. These compounds have been found in both the fruiting bodies and in vitro mycelium of the species. They demonstrate activity against various bacteria, including A. citreus, B. brevis, B. subtilis, E. coli, Leuconostoc mesenteroides, Mycobacterium phlei, Nocardia brasiliensis, P. vulgaris, Pseudomonas fluorescens, S. lutea, S. aureus, and Streptomyces viridochromogenes, along with the fungus Saccharomyces cerevisiae and the yeast Rhodotoula rubra. In the context of cosmetics and skin care, secondary metabolites such as striatins could have potential applications such as antimicrobial and antioxidant effects [47]. Armillaric acid, isolated from mycelial cultures of Armillaria mellea, is a sesquiterpene compound (Table 1) [96]. An aryl

ester of this compound, known as melleolide, has exhibited antibacterial activity [81]. Flammulina velutipes mycelium has produced four sesquiterpenes that possess antibacterial properties: enokipodins A, B, C, and D (Table 1). These compounds are effective against B. subtilis, while enokipodins A and C also demonstrate activity against S. aureus. Enokipodins have a wide range of biological properties that could make them useful in cosmetics, such as their antioxidant effects, skin brightening properties, and anti-inflammatory effects [3; 54]. A steroid named (24Z)-3,11-dioxolanosta-8,24-dien-26-oic acid was extracted from the fruiting bodies of Jahnoporus hirtus (Basidiomycota). This compound is active against Bacillus cereus and Enterococcus faecalis, as reported by Liu *et al*. [71]. Ganomycin A and B, which were isolated from Ganoderma pfeifferi, have shown activity against B. subtilis, Micrococcus flavus, and S. aureus as listed in Table 1.

2.3.2 Peptides

Fungi produce various peptides, one of which is plectasin. It is found in the fruiting bodies of Pseudoplectania nigrella (Ascomycota). Plectasin is categorized as a defensin peptide and has a positive charge. It consists of 40 amino acids and has antimicrobial effects against Gram-positive bacteria such as S. aureus and Streptococcus pneumoniae. Its primary mode of action is destabilizing the cell membranes of these bacteria [87]. In vitro, plectasin's impact on S. pneumoniae mirrors that of penicillin and vancomycin. In addition, this peptide targets Gram-positive bacteria of genera such as Streptococcus (S. pneumoniae, S. pyogenes), Staphylococcus (S. aureus, S. epidermidis), Enterococcus (E. faecalis, E. faecium), Corynebacterium (C. diphtheriae, C. jeikeium), and Bacillus (B. cereus, B. thuringiensis) [14]. Zervamicins are a group of antibacterial peptides produced by Emericellopsis salmosynnnemata (Ascomycota). These linear peptaibols are characterized by a high content of α,α-dialkyl amino acids like α-aminoisobutyric acid [111; 114]. Another set of peptaibols includes peptaibol boletusin, peptaibol chrysospermin-3, and peptaibol chrysospermin-5, all extracted from Boletus spp. These compounds demonstrate efficacy against B. subtilis, Corynebacterium lilium, and S. aureus. Peptaibol chrysospermin-3 also shows activity against various Streptococcus strains [67]. Cyclosporin is a cyclic peptide that is derived from the fungal fermentation of Tolypocladium niveum or Aspergillus terreus strains (Figure 2). It belongs to the cyclosporin family, which comprises cyclic peptides with specific amino acids and has a mild antibiotic effect. However, their primary use is as immunosuppressive agents. Cyclosporin A, for example, is used in medicine to prevent organ rejection in transplant

patients and treat autoimmune diseases [53]. Enniatins, cyclic hexapolypeptides, are synthesized by various strains of Fusarium within the family Nectriaceae (Ascomycota) and possess antibiotic, insecticidal, and anticancer properties [57].

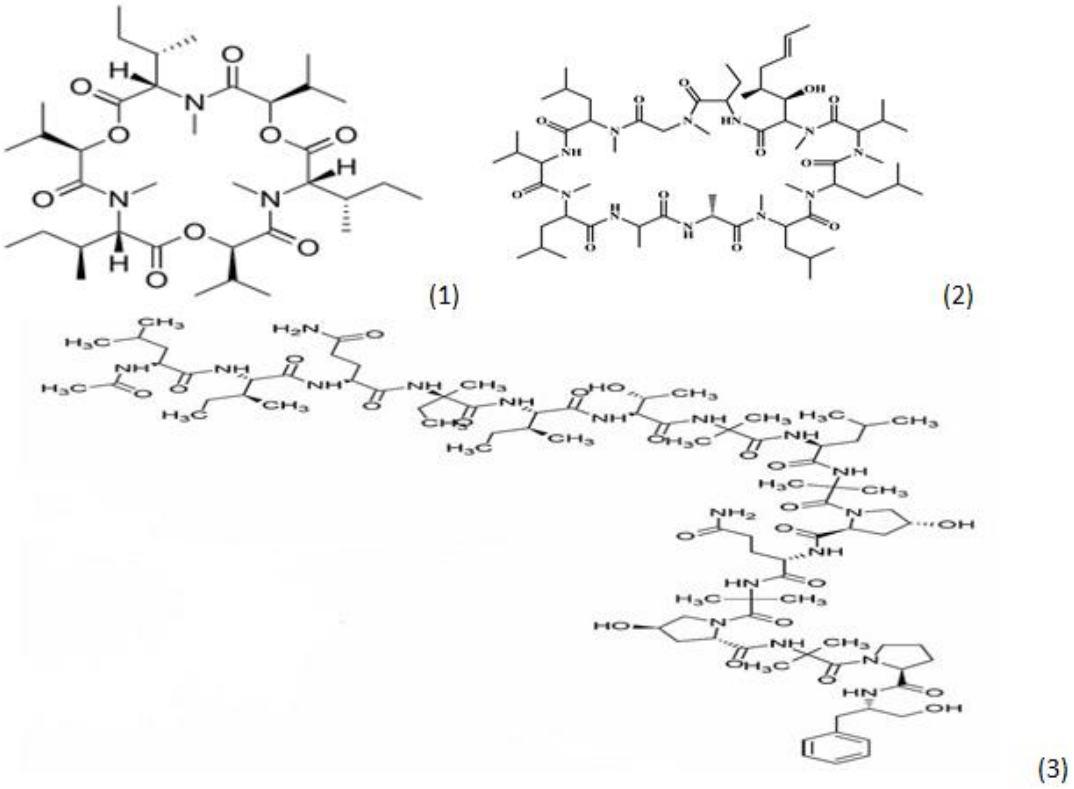


Figure 2. Examples of antibacterial compounds with peptides structure: 1. enniatin; 2. Cyclosporin; and 3. Zervamicin.

An antibacterial nucleoside, nebularine, has been isolated from Clitocybe nebularis, a toxic saprotrophic species [78]. Edible Pleurotus sajor-caju is the source of ribonuclease, an enzyme with antimicrobial, antimitogenic, and antiproliferative effects. It targets RNA and acts against Pseudomonas aeruginosa and S. aureus [92].

2.4 Other Compounds of Fungal Origin with Antibacterial Activity

Pleurotin, a derivative of quinone, along with leucopleurotin and dihydropleurotinic acid, has been isolated from Pleurotus griseus (now classified as Hohenbuehelia grisea). These compounds exhibit activity against Gram-positive bacteria and specific pathogenic fungi. Pleurotin has shown antimicrobial activity against certain bacteria and fungi. In the context of cosmetics, its antimicrobial properties could be explored for potential use as a natural preservative to prevent microbial growth in cosmetic products [115]. Oxalic acid, isolated from the mycelium of Lentinus edodes, shows activity against B. cereus, S. aureus, and E.

faecalis [11]. Oxalic acid derived from fungi presents an array of cosmetic uses due to its exfoliating, brightening, antibacterial, and antioxidant properties [103]. Another compound, cloratin A, a benzoic acid derivative, has been isolated from the saprotrophic inedible fungus Xylaria intracolarata. This compound displays activity against E. coli, Klebsiella pneumonia, P. aeruginosa, and Salmonella enterica, with particularly potent inhibitory activity observed against K. pneumoniae, surpassing the control group [109]. Antibacterial activity is also evident in anthraquinone derivatives such as 6–methylxanthopurpurin-3-O-methyl ether, (1 S, 3 S), austrocortilutein, (1 S, 3 R), austrocortilutein, (1 S, 3 S), austrocortirubin, and torosachryson, isolated from Cortinarius basirubencens. Compounds of erythroglaucine and emodin, isolated from other Cortinarius species, also demonstrated efficacy against S. aureus [10]. A fraction labeled B from Pycnoporus sanguineus, mainly composed of loose-3-one, exhibited activity against S. aureus and various strains of Streptococcus (A, B, C, and G). Compounds isolated from G. pfeifferi showed moderate activity against E. coli, Proteus mirabilis, and Serratia marcescens. Quinoline, isolated from the fungus Leucopaxillus albissimus, showed activity against Achromobacter xyloxidans, Acinetobacter baumannii, Burkholderia cenocepacia, Burkholderia loccose, Burkholderia multivorans, Cytophaga johnsonae, and P. aeruginosa, with the highest activity observed against C. johnsonae [120].

Polysaccharides, such as β-glucans, chitin, and its derivative chitosan, are vital components of the fungal cell wall. Chitosan, featuring amino sugars in its composition, exhibits antibacterial activity. Notably, chitosan is found not only in fungi but also in the shells of arthropods such as crabs, shrimp, squid, and crayfish [94]. Exhibiting a wide antibacterial activity, chitosan proves effective against certain Gram-negative bacteria, Gram-positive bacteria, and fungi. Specifically, it has shown a higher effect on Gram-positive bacteria, including Listeria monocytogenes, Bacillus megaterium, B. cereus, S. aureus, Lactobacillus plantarum, L. brevis, and L. bulgaris. While it does display activity against Gram-negative bacteria, such as E. coli, P. fluorescens, S. typhimurium, and Vibrio parahaemolyticus, its potency is comparatively weaker [23; 64].

Recent studies indicate that chitosan can be obtained biotechnologically from the cell wall of the filamentous fungus Rhizopus oryzae. Its antibacterial properties have been tested against E. coli, K. pneumoniae, and S. aureus [56; 46]. A summary of the antibacterial activity of compounds derived from fungi is provided in Table 2.

Table 2. Summary Of Antibacterial Activity Of Compounds Of Fungal Origin.

Species	Extract	Bacteria	References
Aspergillus giganteus Aspergillus nidulans Aspergillus oryzae Aspergillus parasiticus Aspergillus persicinum Aspergillus flavus Penicillium baculum Penicilium chrysogenum Penicillium turbatum Penicillum chrysogenum	Penicillins	Gram-positive bacteria Diplococcus spp. Enterococcus spp. Staphylococcus spp. Streptococcus spp. Gram-negative bacterial Clostridium spp. Enterobacteriaceae spp.	[13; 82].
Cephalosporium acremonium	Cephalosporins	Gram-positive bacteria: Diplococcus spp. Enterococcus spp. Staphylococcus spp. Streptococcus spp. Gram-negative bacteria: Clostridium spp. Enterobacteriaceae spp.	(25; 72; 34; 60; 35]
Calcarisporium arbuscula Fusidium coccineum Isaria Kogan	Fusidans	Gram-positive bacteria	(25; 118; 34; 72]

Mucor ramannianus			
Fusarium lateritium	Fusafungine	Streptococcus pyogenes Streptococcus pneumoniae Staphylococcus epidermidis Moraxella catarrhalis Legionella pneumophila Mycoplasma pneumonia	[66; 74]
Aspergillus fumigatus Cephalosporium caeruleus Emericellopsis terricola Sarocladium oryzae	Fumigacin (helvolic acid)	Gram-negative bacteria	[134]
Merulius tremellosus	Meridian	Gram-positive bacteria: Arthrobacter citreus Bacillus brevis Bacillus subtilis Corynebacterium insidiosum Sarcina lutea Streptomyces viridochrontogenes Gram-negative bacteria: Proteus vulgaris	[108]
Flagelloscypha pilati	Pilatin	Salmonella typhimurum	[45]
Pleurotellus hypnophillus	Hypnophilin Pleurotellol Pleurotellic acid	Bacillus brevis Salmonella typhimurium	[65]
Lentinellus	Lentinellic acid	Bacillus brevis	[127]

omphalodes Lentinellus Ursinus		Aerobacter aerogenes Corynebacterium insidosum	
Laetiporus sulphureus	Sulphurenic acid Eburicoic acid	Gram-positive bacteria	[125]
Clitopilus passeckerianus	Pleuromutilin	Mycoplasma spp. Brachyspira hyodysenteriae Brachyspira pilosicoli	[95]
Cyathus striatus	Striatins A, B, C	Arthrobacter citreus Bacillus brevis Bacillus subtilis Escherichia coli Leuconostoc mesenteroides Mycobacterium phlei Nocardia brasiliensis Proteus vulgaris Pseudomonas fluorescens Sarcina lutea Staphylococcus aureus Streptomyces viridochromogenes	[47]
Armillaria mellea	Armillaria acid	Gram-positive bacteria	[96]
Flammulina velutipes	Enokipodin	Bacillus subtilis Staphylococcus aureus	[54]
Jahnoporus hirtus	(24Z)-3,11-Dioxolanosta-8,24-dien-26-oic acid	Bacillus cereus Enterococcus faecalis	[71]
Ganoderma pfeifferi	Ganomycin A	Bacillus subtilis Micrococcus flavus Staphylococcus aureus	[85]
Pseudoplectania nigrella	Plectasin	Bacillus cereus Bacillus thuringiensi	[87; 14]

		Corynebacterium diphtheriae Corynebacterium jeikeium Enterococcus faecalis Enterococcus faecium Staphylococcus aureus Staphylococcus epidermidis	
Clitocybe nebularis	Nebularine	Mycobacterium tuberculosis	[78]
Pleurotus sajor–caju	Ribonuclease	Pseudomonas aeruginosa Staphylococcus aureus	[92]
Gymnophilus spectabilis	Hepta-4,6-diyn-3-ol 7-Chloro-hepta-4,6-diyn-3-ol	Gram-positive/Gram-negative	[8]
Hohenbuehelia grisea	Pleurotin	Gram-positive bacteria	[115]
Albatrellus flettii	Confluent Grifolin Neogrifolin	Bacillus cereus Enterococcus faecalis	[71]
Lentinula edodes	Oxalic acid	Bacillus cereus Staphylococcus aureus Streptococcus faecalis	[11]
Cortinarius basirubencens	Austrocortilutein Austrocortilutein Austrocortirubin Torosachryson	Staphylococcus aureus	[10]
Boletus spp.	Boletusin Chrysospermin	Bacillus subtilis Corynebacterium lilium Staphylococcus aureus	[67]
Pycnoporus sanguineus	Phenoxazin-3-one	Staphylococcus aureus Streptococcus spp.	[120]
Ganoderma	Terpenes	Escherichia coli	[85]

pfeifferi		Proteus mirabilis Serratia marcescens	
Xylaria intracolarata	Cloratin A	Escherichia coli Klebsiella pneumonia Pseudomonas aeruginosa Salmonella enteritidis	[109]
Leucopaxillus albissimus	Crinoline	Achromobacter xyloxidans Acinetobacter baumannii Burkholderia cenocepacia Burkholderia loccose Burkholderia multivorans Cytophaga johnsonae Pseudomonas aeruginosa	[120]

2.4.1 Extracts of Fungal Origin with Antibacterial Activity

A considerable number of studies have focused on evaluating the antibacterial activity of natural raw materials, often by investigating the analysis of complete extracts. Notably, several types of extracts have been extensively examined, including aqueous, ethanol, methanol, chloroform, dichloromethane, ether, and acetone extracts.

Ganoderma lucidum stands as a prominent fungal raw material in East Asian traditional medicine, including TCM [104]. Notably, diverse extracts including aqueous, ethanol, methanol, and acetone have demonstrated comparable efficacy against gentamicin sulfate, an aminoglycoside antibiotic. This effectiveness extends to various bacterial species: E. coli, S. aureus, K. pneumoniae, B. subtilis, S. typhimurium, and P. aeruginosa [110]. Other studies have confirmed that acetone extract of G. lucidum exhibits antibacterial activity, mainly against Gram-negative K. pneumoniae bacteria. Additionally, a synergistic interaction was observed when combining G. lucidum extracts with antimicrobial agents such as ampicillin, cefazolin, oxytetracycline, and chloramphenicol. This synergy was particularly pronounced with cefazolin against B. subtilis and Klebsiella oxytoca [142]. Conversely, a chloroform extract from the edible mycorrhizal fungus Hygrophorus agathosmus exhibited inhibition against various pathogenic bacteria, including E. coli, Enterobacter aerogenes, S. typhimurium, P. aeruginosa, S. aureus, S. epidermidis, and B. subtilis. Furthermore, this

extract demonstrated inhibitory effects on Candida albicans and S. cerevisiae [140]. In a similar vein, a dichloromethane extract from Suillus collitinus observed activity against Gram-positive bacteria, including S. epidermidis and B. subtilis. This extract demonstrated significant antibacterial activity with MIC values of 7.81 µg/mL, surpassing the reference antibiotic streptomycin (MIC = 15.62 µg/mL). The MIC values for S. aureus remained the same as those of streptomycin at 15.62 µg/mL [140]. Finally, the methanolic extract of Hypholoma fasciculare, a saprotrophic poisonous fungus, exhibited notable antibacterial activity against Gram-positive bacteria such as B. cereus, B. subtilis, and S. aureus. Turkoglu [135] conducted a study investigating the antibacterial activity of ethanol extracts from L. sulphureus. The extract displayed inhibitory activity against the growth of Gram-positive bacteria, including B. subtilis, B. cereus, Micrococcus luteus, and M. flavus. Another study analyzed the antibacterial activity of different extracts (chloroform, ethyl acetate, and water) from Lentinula edodes fruiting bodies. These extracts showed antibacterial activity against Streptococcus spp., Actinomyces spp., Lactobacillus spp., Prevotella spp., and Porphyromonas spp., which are known to cause various oral infections. Specifically, chloroform extracts exhibited bactericidal activity against both growing and resting bacterial cells of Streptococcus mutans and Prevotella intermedia, while the other two extracts exhibited bacteriostatic activity against both growing and resting bacterial cells of S. mutans and resting bacterial cells of P. intermedia. Furthermore, a low molecular weight fraction study was conducted on an extract of L. edodes formulated as a mouthwash and administered to a group of volunteers [124]. Methanolic extract from the mycelium of Leucopaxillus giganteus, an inedible saprophytic species, showed antibacterial properties against Gram-positive bacteria in the order of potency: S. aureus > B. cereus > B. subtilis. This study also revealed that diammonium hydrogen phosphate was the preferred nitrogen source for enhancing the production of bioactive compounds inhibiting the growth of Gram-positive bacteria [9]. Studies on methanolic extracts of Phellinus rimosus and Navesporus loccose demonstrated moderate antibacterial activity against Gram-positive bacteria B. subtilis and S. aureus. Ethanolic extracts from Pleurotus ostreatus and Meripilus giganteus exhibited broad-spectrum antibacterial activity, particularly against S. lutea [58]. Evaluating extracts from fruiting bodies and mycelial cultures of Trametes versicolor, researchers found varying antibacterial activity based on the type of solvent used for the extraction (water, organic solvents, or mixtures). The study revealed significant antibacterial activity against Gram-positive bacteria, with lower activity against Gram-negative bacteria. This effect was attributed to coriolin, a sesquiterpene compound found in Trametes (formerly Coriolus) spp.

(Table 1). Extracts from Clavariadelphus loccose and T. versicolor have exhibited activity against a range of bacteria, including E. coli, E. aerogenes, S. typhimurium, S. aureus, and B. subtilis [140]. Aqueous extracts of Cordyceps sinensis and Cordyceps militaris, which are species that parasitize invertebrates, have demonstrated antibacterial activity against S. aureus, probably as a result of an increase in phagocytic macrophage activity and cytokine expression [58]. Ethanol extracts containing polysaccharides from Grifola floccose fruiting bodies have been tested against Gram-positive bacteria such as S. aureus, E. faecalis, B. cereus, L. monocytogenes, and Gram-negative bacteria such as E. coli, Salmonella enteritidis, Shigella sonnei, and Yersinia enterocolitica. The most notable antibacterial activity was observed against B. cereus [61]. Acetyl acetate extracts from various species growing in Brazil, including Phellinus sp., Gloeoporus thelephoroides, Hexagonia hydnoides, and Nothopanus hygrophanus, demonstrated inhibition of growth against bacteria such as B. cereus, L. monocytogenes, and S. aureus [113]. Aqueous, ethanol, methanol, and xylene extracts of Agaricus bisporus and P. sajor-caju, both saprophytic edible fungi, have shown antibacterial activity against E. coli, E. aerogenes, P. aeruginosa, and K. pneumoniae. Consumption of these fungi may provide natural protection against common pathogenic organisms [132]. Methanolic extracts of Hydnum repandum, an edible saprophytic species, have demonstrated activity against the Gram-negative bacteria P. aeruginosa [101]. The methanolic extract of the fruiting bodies of Lepista nuda, another edible fungus, exhibited antibacterial activity against E. coli and P. aeruginosa [28]. Dichloromethane extract from S. collitinus displayed activity against a range of bacteria, including E. coli, E. aerogenes, S. typhimurium, S. aureus, and S. epidermidis, B. subtilis, as well as C. albicans and S. cerevisiae (Yamac and Bilgili, 2006; Alves *et al*., 2012). Regarding L. sulphureus, both ethanolic and aqueous extracts from its fruiting bodies have shown antibacterial effects against various strains, including B. subtilis, B. cereus, M. luteus, M. flavus, and K. pneumoniae. Among these strains, M. flavus exhibited the highest susceptibility, while K. pneumoniae showed resistance. Although the efficacy of the active extracts was lower compared to commercial drugs, they still demonstrated potential as antibacterial agents. Furthermore, the aqueous extract of L. sulphureus fruiting bodies has shown antibacterial effects against M. flavus and L. monocytogenes [135]. Notably, the extract displayed significant efficacy against L. monocytogenes, a strain resistant to streptomycin. A summary of the antibacterial activity of fungal extracts can be found in Table 3.

Table 3. Summary of antibacterial activity of fungal origin extracts.

Species	Extract	Bacteria	References
Ganoderma lucidum	Acetone extract Aqueous extract Ethanol extract Methanol extract	Bacillus subtilis Escherichia coli Klebsiella pneumoniae Pseudomonas aeruginosa Salmonella typhimurium Staphylococcus aureus	[110]
Ganoderma lucidum	Acetone extract	Bacillus subtilis Klebsiella oxytoca	[142]
Hygrophorus agathosmus	Chloroform extract	Bacillus subtilis Enterobacter aerogenes Escherichia coli Pseudomonas aeruginosa Salmonella typhimurium Staphylococcus aureus Staphylococcus epidermidis	[140]
Suillus collins	Dichloromethanol extract	Bacillus subtilis Staphylococcus epidermidis	[140]
Hypholoma fascicular	Methanol extract	Bacillus cereus Bacillus subtilis Staphylococcus aureus	[9]
Laetiporus sulphureus	Ethanol extract	Bacillus cereus Bacillus subtilis Micrococcus flavus Micrococcus luteus	[135]
Lentinula edodes	Chloroform extract Acetate-ethyl extract	Actinomyces spp. Lactobacillus spp. Porphyromonas spp. Prevotella spp. Streptococcus spp.	[58]
Leucopaxillus giganteus	Methanol extract (mycelial cultures)	Bacillus cereus Bacillus subtilis Staphylococcus aureus	[9]
Navesporus floccose Phellinus rimosus	Methanol extract	Bacillus subtilis Staphylococcus aureus	[123]
Pleurotus ostreatus Meripilus giganteus	Ethanol extract	Sarcina lutea	[58]
Trametes versicolor	Methanol extract	Gram-positive bacteria	[46]
Grifola frondosa	Ethanol extracts/polysaccharides	Bacillus cereus	[61]
Gloeoporus thelephoroides Hexagonia hydroxides	Acetate-ethyl extract	Bacillus cereus	[113]

Phellinus spp.			
Nothopanus hygrophanus	Acetate-ethyl extract	Listeria monocytogenes Staphylococcus aureus	[113]
Agaricus bisporus Pleurotus sajor–caju	Aqueous extract Ethanol extract Methanol extract Xylene extract	Enterobacter aerogenes Escherichia coli 390 Escherichia coli 739 Klebsiella pneumoniae Pseudomonas aeruginosa	[132]
Hydnum repandum	Methanol extract	Pseudomonas aeruginosa	[101]
Lepista nuda	Methanol extract	Escherichia coli Pseudomonas aeruginosa	[28]
Suillus collins	Dichloromethane extract	Bacillus subtilis Candida albicans Enterobacter aerogenes Escherichia coli Salmonella typhimurium Staphylococcus aureus Staphylococcus epidermidis	[140]
Hygrophorus agathosmus	Chloroform extract	Bacillus subtilis Enterobacter aerogenes Salmonella typhimurium Staphylococcus aureus Staphylococcus epidermidis	[4]
Laetiporus sulphureus	Ethanol extract Aqueous extract	Bacillus subtilis Bacillus cereus Micrococcus luteus Micrococcus flavus Klebsiella pneumoniea Listeria monocytogenes	[135]

Nandika *et al*. [89] extracted the chemical components of a fungus comb from Indomalayan termite (*Macrotermes gilvus* Hagen) (Isoptera: Termitidae) and identified them as phenol, hydroquinone, steroids, terpenoids, and saponin compounds. In addition, the ethyl acetate extract inhibited the growth of *Aspergillus foetidu*s, a fungus that attacks wooden raw materials, including rubberwood (*Hevea brasiliensis* Muell. Arg.). The bioactivity of fungus comb extract from Indomalayan termite (*M. gilvus* Hagen) mounds as an antifungal and antibacterial agent has not been reported as much. A similar study revealed that fungus comb extracts, especially ethyl acetate, could be considered as a new antimicrobial agent after *n*-hexane, ethyl acetate, methanol, and water extracts were obtained from fungus combs isolated from Indomalayan termite (*Macrotermes gilvus* Hagen) mound. Their antibacterial and antifungal activities against food spoilage microorganisms including *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa ATC*C 27853, *Staphylococcus aureus ATCC* 25923,

Aspergillus flavus, and *Aspergillus niger* were evaluated by Kirby–Bauer disc diffusion and microdilution. Results showed that ethyl acetate extract formed the largest diameter inhibition zone for all tested bacteria and fungi, and exhibited antibacterial activity against all tested bacteria with minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of 0.39 and 0.78 mg/mL, respectively, and suppressed *A. flavus* and *A. niger* with an MIC value of 0.78 mg/mL. This extract contained guaiacol and syringol, which were predicted as the main antimicrobial components in fungus comb. *n*-Hexane extract only inhibited Gram-positive bacteria. *S. aureus ATCC* 25923 was the most sensitive to all the extracts, and *A. flavus* was more sensitive than *A. niger* [73].

2.5 Anti-fungal

Antifungal Activity of Substances of Fungal Origin

2.5.1. Compounds of Fungal Origin with Antifungal Activity

Due to concerns over the toxicity of polyene antibiotics and synthetic azole derivatives, researchers have turned to exploring natural compounds with antifungal properties. This pursuit is driven by the increasing resistance of Candida species to traditional antifungal drugs, prompting the search for alternative resources. The antifungal activity of substances produced by fungi is attributed to high-molecular-weight compounds such as proteins and peptides, as well as low-molecular-weight compounds, including terpenes (sesquiterpenes), steroids, and organic acids [21]. Numerous studies conducted in this field involve screening extracts derived from fungal materials show that Biforminic acid and biformin, a polyacetylene compound, are examples of substances with antifungal properties produced by the saprophytic fungus Trichaptum biforme. These compounds were among the earliest bioactive substances of fungal origin to be identified [63]. Griseofulvin is an antibiotic used for treating fungal infections in both humans and animals. Its mechanism of action involves inhibiting the cell divisions of dermatophytes belonging to the genera Microsporum, Epidermophyton, and Trichophyton. Griseofulvin is produced by various species of the Penicillium genus, particularly Penicillium griseofulvum, Penicillium aethiopicum, Penicillium janezewski, and Penicillium lanosus. Commercial production of griseofulvin involves biotechnological methods using Penicillium patulum [27; 86]. During the fermentation processes leading to griseofulvin synthesis, other metabolites are formed, primarily intermediates in the antibiotic's production, such as dehydrogriseofulvin, griseophenone A, griseoxanthone C, griseophenone Y, and dechlorogriseofulvinic acid.

These metabolites might have significant implications in the search for new therapeutic agents. Griseofulvin's mechanism of action involves inhibiting RNA biosynthesis and chitin synthesis, leading to damage to the fungal cell wall. It is commonly used for treating fungal skin, nail, and hair infections. When administered orally, it is well absorbed from the gastrointestinal tract and reaches peak concentration after about 4 h. The half-life of griseofulvin is 16–20 h, and the recommended dosage for treating superficial infections is typically 250 mg every 6 h. However, it is worth noting that griseofulvin has been discontinued from use [27; 86]. Agrocybin, a peptide displaying activity against plant pathogens such as Mycosphaerella arachidicola and Fusarium oxysporum, was isolated from the fruiting bodies of Agrocybe cylindracea, a saprophytic Basidiomycota species [91].

Also, screening studies aimed at identifying naturally occurring fungicides from fungi have demonstrated the potent antifungal impact of the ethanolic extract derived from the fruiting bodies of Albatrellus dispansus. Grifolin, the active compound isolated from these bodies, has been identified as the crucial component. Against Erysiphe graminis, Sclerotinia sclerotiorum, and Fusarium graminearum, it exhibited antifungal activity levels of 86.4% and 80.9%, respectively, at a concentration of 304.9 μM [75]. Cloratin A, sourced from X. intracolarata, displayed activity against Aspergillus niger (with an inhibition zone diameter of 15 mm) and C. albicans (with an inhibition zone diameter of 17 mm), comparable to the control substance nystatin, which also had an inhibition zone diameter of 17 mm. The diameter of the inhibition zone (IZD) serves as a reliable indicator of the antifungal activity present in the sample [4]. Lactarius rufus, an inedible mycorrhizal fungus, accumulates the sesquiterpene rufuslactone, an isomer of the previously described 3,8-oxa-13-hydroxylactar-6-en-5-lactaric acid γ-lactone from Lactarius necator. Rufuslactone exhibits antifungal properties against plant pathogens such as Alternaria alternata, Alternaria brassicae, Botrytis cinerea, and Fusarium graminearum [75]. Sesquiterpenoids Enokipodins F, G, and I were isolated from the mycelium of F. velutipes, a saprotrophic tree species. These compounds exhibit moderate activity against A. fumigatus, a pathogenic species affecting mammals, birds, and insects [54]. A summary of the antifungal activity of fungal compounds is presented in Table 4.

Table 4. Summary of antifungal activity of compounds of fungal origin.

Species	Chemical Compound/Extract	Fungal Pathogen	Reference
Trichaptum biforme	Biforminic acid Biformin	Aspergillus niger	[63]
Penicillium spp.	Griseofulvin	Epidermophyton Microsporum Trichophyton	[27]
Agrocybe cylindracea	Agrocybin	Fusarium oxysporum Mycosphaerella arachidicola	[91]
Cordyceps militaris	Cordymin	Bipolaris maydis Candida albicans Mycosphaerella arachidicola Rhizoctonia solani	[139]
Lactarius rufus	Rufuslactone	Alternaria alternata Alternaria brassicas Botrytis cinerea Fusarium graminearum	[75]
Flammulina velutipes	Enokipodins F, G, I	Aspergillus fumigatus	[54]
Tricholoma giganteum	Trichogin	Fusarium oxysporum Mycosphaerella arachidicola Physalospora piricola	[42]
Gloeophyllum sepiarium	Oospolactone	Alternaria spp. Fusarium spp. Giberella spp. Penicilim spp. Aspergillus spp.	[88]
Lentinula edodes	Lentin	Mycosphaerella	[92]
Pleurotus eryngii	Eryngin	Fusarium oxysporum Mycosphaerella arachidicola	[137]
Hypsizigus marmoreus	Hypsin	Botrytis cinerea Fusarium oxysporum Mycosphaerella arachidicola Physalospora piricola	[83]
Strobilurus tenacellus	Strobilurins	Aspergillus panamensis Candida albicans Paecilomyces variety Penicillium notatum Rhodotorula glutinis	[36]
Hygrophorus chrysodon	Chrysotriones A, B	Fusarium verticillioides	[38]
Ganoderma annulare	5-Ergost-7-en-3-ol 5-Ergosta-7,22-dien-3-ol	Microsporum canis Trichophyton	[126]

	5,8-Epidioxy-5,8-ergosta-6,22-die -3-ol Applanoxidic acids A, C, F, G, H	mentagrophytes	
Ganoderma lucidum	Ganoderma	Botrytis cinerea Fusarium oxysporum Physalospora paricola	[36]
Pleurotus sajor–caju	Ribonuclease	Fusarium oxysporum Mycosphaerella arachidicola	[92]
Crepidotus fulvifibrillosus	Strobilurins	Alternaria porri Aspergillus ochraceus Candida albicans Cladosporium cladosporioides Curvularia lunata Epicoccum purpurascens Mucor miehei Nematospora coryli Neurospora crassa Paecilomyces varioti Penicillium islandicum Penicillium notatum Phoma clematidina Phytophthora infestans	[128]

2.5.2 Extracts of Fungal Origin with Antifungal Activity

The antifungal activity of both aqueous and ethanol extracts from A. bisporus was determined against A. flavus. Ethanolic extracts and the protein fraction obtained from the mycelium of Ophiocordyceps sobolifera displayed potent antifungal effects against both pathogenic and saprophytic fungi, including C. albicans [116]. Methanolic extracts of A. bisporus, Agaricus torques, and Agaricus sylvicola demonstrated antifungal activity against C. albicans and Candida tropicalis (Öztürk *et al*., 2011). The chloroform extract of H. agathosmus exhibited antifungal activity against S. cerevisiae [140]. Additionally, the dichloromethane extract from S. collitinus showed activity against both S. cerevisiae and C. albicans [140]. Also, numerous fungal fruiting body extracts have been tested for their antifungal activity against C. albicans strains. Notably, the ethanolic extract derived from L. sulphureus fruiting bodies exhibited significant activity, with an inhibition zone diameter (IZD) measuring 21 ± 1 mm. This result surpassed the positive control, nystatin, which had an IZD of 19 mm [135] and so on. A summary of the antifungal activity of fungal extracts is provided in Table 5.

Table 5. Summary of Antifungal Activity of Extracts of Fungal Origin.

Species	Extract	Fungal Pathogen	Reference
Albatrellus dispansus	Ethanol extract	Erysiphe graminis Sclerotinina sclerotiorum Fusarium graminearum	[75]
Agaricus bisporus	Aqueous extract Ethanol extract	Aspergillus flavus	[130]
Ophiocordyceps sobolifera	Ethanol extract	Candida albicans	[116]
Agaricus bisporus Agaricus torques Agaricus sylvicola	Methanol extract	Candida albicans Candida tropicalis	[102]
Hygrophorus agathosmus	Chloroform extract	Saccharomyces cerevisae	[140]
Suillus collitinus	Dichloromethane extract	Candida albicans Saccharomyces cerevisae	[140]
Ganoderma lucidum	Ethanol extract	Aspergillus fumigatus Aspergillus versicolor Aspergillus ochraceus Aspergillus niger Trichoderma viride Penicillium funiculus Penicillium ochrochloron Penicillium verrucosum	[142]
Laetiporus sulphureus	Ethanol extract Aqueous-ethanol extract	Candida albicans Aspergillus niger Botrytis cinerea Fusarium oxysporum, Penicillium gladioli Sclerotinia sclerotiorum	[135]
Lactarius camphoratus	Methanol extract	Candida albicans	[9]
Lentinula edodes	Chloroform extract	Candida albicans	[11]
Lepista nuda	Methanol extract	Candida albicans	[28]
Trametes versicolor	Methanol extract	Aspergillus fumigatus	[46]

According to Al-Saleem *et al*. [3], showing that *P. chrysogenum* extract exhibited significant antifungal activity towards *Candida albicans* and *Cryptococcus neoformans* with MIC 93.75 ± 0.55 and 19.53 ± 0.48 µg/mL, respectively. Moreover, kojic acid (156) revealed the same potency towards *Fusarium oxysporum* and *Cryptococcus neoformans* with MIC 39.06 ± 0.85 and 39.06 ± 0.98 µg/mL, respectively.

Holzknecht *et al*. [48] also reported that the antifungal protein C (PAFC) produced by *P. chrysogenum* Q176 was produced together with PAF and PAFB into the culture broth. Recombinant PAFC's functional characterization revealed a promising novel molecule for anti-*Candida* therapy. In pre-established biofilms of two strains of *C. albicans*, the planktonic cells were killed by the thermotolerant PAFC while the sessile cells' metabolic activity decreased. One of the strains was a fluconazole-resistant one that displayed greater PAFC sensitivity than the fluconazole-sensitive one. The absence of hemolytic activity supports the further use of PAFC in clinical therapy.

Furthermore, Huber *et al*. [50] found that PAF and PAFB, the antimicrobial proteins (AMPs) secreted by the filamentous fungus *P. chrysogenum* Q176, are highly stable due to a compact disulfide-bond, β-fold structure. In micromolar doses, these two AMPs effectively prevented the growth of several fungi including *Aspergillus fumigatus*, *Trichophyton spp., Aspergillus niger*, and *Candida spp.*, along with the *Neurospora crassa* and *Saccharomyces cerevisiae.*, which were vulnerable to both proteins since their growth diminished at 0.25–4 μM PAF or PAFB doses, respectively.

2.6 Anti-viral

2.6.1 Extracts and Chemical Compounds of Fungal Origin with Antiviral Activity

The antiviral mechanisms of fungal-derived substances often involve blocking viral enzymes, disrupting nucleic acid synthesis, or indirectly boosting the immunostimulatory effects. While numerous chemical compounds with proven antiviral activity are registered drugs, ongoing intensive research aims to search for substances of natural origin, including those of fungal origin. The scientific literature broadly describes the antiviral effect of both fruiting body extracts and single, isolated compounds [70]. For instance, triterpenes such as ganoderiol, ganodermanontriol (Table 1), and ganodermic acid derived from G. lucidum exhibit activity against HIV-1 [36]. Similarly, ganodermadiol, lucidadiol, and lucidumol B obtained from Ganoderma Pfeifer demonstrate effectiveness against the influenza A virus. Ganodermadiol also combats the herpes virus HSV-1 [36]. Phenolic compounds sourced from Inonotus hispidus exhibit activity against influenza viruses of types A and B. Among the macromolecular compounds with antiviral activity isolated from fungi, the most noteworthy is the PSK complex (Krestin). This polysaccharide peptide, derived from the mycelium of T. versicolor, boasts anticancer and immunostimulatory properties. Scientific studies have

confirmed the antiviral activity of PSK against cytomegalovirus and its ability to inhibit HIV replication [133].

In the study of natural substances, special attention has been given to the analysis of aqueous extracts. This is attributed to the logistical challenges and potential hazards associated with the utilization of organic solvents as extraction agents for raw materials. Compounds found within the fruiting bodies of species such as G. pfeifferi, Rozites caperata, and Agaricus brasiliensis have exhibited activity against herpes viruses. Notably, sulfated polysaccharides from A. brasiliensis, RC28 proteoglycan from R. caperata, and triterpenoids from G. Pfeiffer (present in aqueous extracts) exhibit noteworthy antiviral potential. These compounds hold the ability to effectively counteract various stages of herpes virus replication [85; 16; 141].
Aqueous extracts containing polysaccharides and ethanol extracts sourced from Pleurotus pulmonarius fruiting bodies have demonstrated antiviral activity against the influenza A (H1N1pdm) virus (Vlasenko *et al.*, 2020). Similarly, the acidic polysaccharide fraction obtained from C. militaris fruiting bodies has shown identical antiviral activity against the influenza A (H1N1) virus [97].

In addition, asqueous–methanol extracts derived from the fruiting bodies of L. sulphureus have demonstrated inhibitory effects on HIV reverse transcriptase. This enzyme plays a crucial role in the transcription process, and its inhibition leads to the suppression of virus replication. The observed antiviral activity within the tested extracts is believed to be influenced by the presence of immunomodulatory polysaccharides [84]. In the case of polysaccharides EP-AV1 and EP-AV2 sourced from an aqueous extract of the fruiting body of Porodaedalea pini (also known as Phellinus pini), their presence inhibits plaque formation in Vero cells induced by herpes simplex virus 1 (HSV-1) and by Coxsackie virus B3 (CVB3) in HeLa cells. These polysaccharides have been demonstrated to affect the initial stage of virus replication [67].

Polyphenols were isolated from the ethanol extract of the fruiting bodies of Phellinus baumii. Through spectroscopic techniques, compounds including hesperidin, hypholomine B, inoscavin A, davallialactone, and pelligridin D were identified. These compounds demonstrated inhibitory effects on the neuraminidase activity, an enzyme specific to the H1N1, H5N1, and H3N2 strains of the influenza virus. Additionally, they exhibited a reduction in the virus-induced cytopathic effect (CPE). Neuraminidase serves as an enzyme that allows viruses to exit cells by breaking down the cell membrane of an infected cell. It

also plays a role in facilitating virus attachment to cell membranes, aiding their entry into the cell due to its high affinity for the sialic acid of membrane receptors [52]. Laccase isolated from Pleurotus ostreatus and tyrosinase from A. bisporus show activity against HCV. Laccase from P. ostreatus has been shown to block viral entry and replication into PBMC and HepG2 cells, while tyrosinase from A. bisporus inhibits viral replication into replicon-containing Huh-5-2 cells [121]. Another noteworthy species that show significant antiviral activity is Grifola frondosa. The main active compound is β-glucan (GF-D). It has been shown that a combination of GF-D with IFN human interferon α–2b could potentially offer effective therapy against chronic HBV infections [40; 44].

In 2018, structural identification of lentinan from L. edodes mycelium LNT-1 was conducted, followed by an investigation of its antiviral activity against hematopoietic necrosis virus (IHNV) [112]. Notably, its immunostimulatory activity was also demonstrated. As proven, the innate immune response is a critical factor in the course of COVID-19 disease. COVID-19 patients show high titers of inflammatory cytokines, so the effect of LNT-1 on SARS-CoV-2 should be considered [121].

Furthermore, a potential candidate in the battle against SARS-CoV-2 is Inonotus obliquus, commonly known as the chaga fungus, which possesses a robust enzyme system and defense mechanism due to its parasitic lifestyle [121]. SARS-CoV-2, the virus responsible for COVID-19, primarily targets the human respiratory system and other vital organs. Currently, no specific treatment for SARS-CoV-2 infection exists, although certain drugs have displayed potential efficacy in inhibiting the virus. Natural substances, including fungi, have exhibited potent antiviral and anti-inflammatory effects positioning them as promising candidates for effective COVID-19 treatments [121]. I. obliquus, commonly found in Asia, Europe, and North America, serves as a widely utilized natural resource for various ailments. A specific polysaccharide fraction derived from I. obliquus, named IOP, has shown the ability to inhibit the production of NO and similar cytokines associated with COVID-19. COVID-19 patients often experience inflammatory responses, resulting in elevated plasma levels of cytokines and leukocytes. Since IOPs have shown promising results in treating various viral diseases, their potential effect on COVID-19 infection holds considerable promise. Furthermore, an aqueous extract of I. obliquus has demonstrated virucidal activity against the hepatitis C virus, remarkably reducing its infectivity by 100-fold within 10 min [77]. A summary of the antiviral activity of compounds and fungal extracts is provided in Table 6.

Table 6. Summary of Antiviral Activity of Compounds and Extracts of Fungal Origin.

Species	Chemical Compound/Extract	Virus Type	Reference
Tricholoma giganteum	Trichogin	HIV-1	[42]
Ganoderma lucidum	Ganoderiol Ganodermanontriol Ganodermic acid	HIV-1	[36]
Ganoderma pfeiferi	Ganodermadiol	H1N1	[85]
Inonotus hispidus	Phenolic compounds	H1N1and B	[2]
Trametes versicolor	PSK complex	Cytomegalovirus HIV	[133]
Agaricus brasiliensis	Aqueous extracts	HSV	[32]
Rozites caperata	Aqueous extracts	HSV	[141]
Ganoderma pfeifferi	Aqueous extracts	HSV	[85]
Pleurotus pulmonarius	Ethanol extract	(H1N1pdm)	[136]
Cordyceps militaris	Polyssaccharide acidic fraction	H1N1	[97]
Laetiporus sulphureus	Aqueosus-methanol extract	HIV	[30]
Agaricus brasiliensis	Polysaccharides	PV-1	[16]
Porodaedalea pini	EP-AV1 polysaccaride EP-AV2 polysaccaride	HSV-1 CVB3	[93]
Phellinus baumii	Hispidin Hypholomine B Inoscavin A Davallialactone Phelligridin D	H1N1, H5N1, H3N2	[52]
Agaricus bisporus Pleurotus ostreatus	Laccase enzyme Tyrosinase enzyme	HCV	[121]
Grifola frondosa	B-glucan	HBV	[40]
Lentinula edodes	Lentinan	IHNV	[112]
Inonotus obliquus	Polysaccharide fraction Aqueous extract	COVID-19 HCV	[121]

In vitro as well as in vivo studies by Huber *et al*. [50] on PAF and PAFB, the two antimicrobial proteins (AMPs) secreted by the filamentous fungus *P. chrysogenum* Q176,

displayed that they had antiviral activity without triggering any cytotoxic effects or hemolytic activity on mammalian cells. Experiments in human cervix cancer cells showed that they both reduced Human Coronavirus cytopathogenic effects. It was the very first study on the antiviral ability of small, cysteine-rich and cationic proteins derived from fungi.

Study by Peng *et al*. [105] isolated sorbicatechol A and sorbicatechol B (146,147), from the deep-sea sediment-derived fungus *P. chrysogenum* strain PJX-17's culture. Results revealed that both displayed activities against influenza virus A (H1N1), with IC_{50} at 85 and 113 μM, respectively.

2.7 Antimicrobial

According to Newaz *et al*. [90], several compounds were isolated from the Indonesian mangrove sediment-derived fungus *P. chrysogenum* ZZ1151. The new peniprenylphenol A (200) was found to possess promising antimicrobial activity towards the human pathogens MRSA, *E. coli* and *C. albicans* with MIC values of 6, 13, and 13 mg/mL, respectively. In addition, the other known isolated compounds, preparaherquamide (203), uridine (205) and 4-hydroxybenzeneacetic acid methyl ester (207) revealed antimicrobial activity with MIC values in a range from 3 to 25 mg/mL towards the three pathogens. Meanwhile thymine (204) and clavatol (206) demonstrated antibacterial activity against MRSA and *E. coli* only with MIC values of 13–25 mg/mL and 2-hydroxyphenylacetic acid methyl ester (209) showed activity against both MRSA and *C. albicans* with MIC values of 13 and 7 mg/mL, respectively. Also, penicimumide (201) showed antibacterial activity against *E. coli* (13 mg/mL), communal G (102) and 4-hydroxyphenylethanone (210) had activity against MRSA (MIC: 25 mg/mL) and 2,5-dihydroxyphenylacetic acid methyl ester (208) exhibited antifungal activity against *C. albicans* (MIC = 25 mg/mL).

Orfali *et al*. [100] conducted a study on compounds (177–181) obtained from the fungus P. chrysogenum that was found in Wadi Lajab sediment. The research aimed to investigate the antimicrobial activity of these compounds against five pathogenic bacteria, namely Staphylococcus aureus, Bacillus licheniformis, Escherichia Ferguson, Enterobacter xiangfangensis, and Ps. aeruginosa. The results indicated that all samples, except 6-hydroxymellein (179), demonstrated selective activities towards Gram-positive bacteria, Staph. aureus and B. licheniformis, with MIC values ranging from 0.8 to 21.6 μg/mL. Notably, 4-chloro-6-hydroxymellein (180) exhibited a highly potent effect towards Gram-

positive bacteria, with MIC values of 1.00 and 0.8 µg/mL for Staph. aureus and B. licheniformis, respectively.

A study by Chang *et al*. [19] on tyrosol (242) isolated from *P. chrysogenum* DXY-1, obtained from deep-sea sediments nearby the East Sea, found that tyrosol had an anti-quorum sensing (anti-QS) activity. All studies implied that tyrosol (242) may act as a possible inhibitor for the QS systems to resolve the frightening crisis of bacterial resistance. It may be used as a QS inhibitor against *C. violaceum* and *Ps. aeruginosa.* The docking outcomes showed that it inhibited the QS system of CviR in *C. violaceum* by binding to the DNA-binding domain and blocking pathogenic gene expression**.**

Zhen *et al.* [145], treated chrysoxanthones A-C (161–163) obtained from the *P. chrysogenum* HLS111 strain with the histone-deacetylase inhibitor VPA. They were examined against *Staph. epidermidis* (ATCC 12,228, MSSE), *B. subtilis* (ATCC 63,501), *Staph. aureus* (ATCC 29,213, MSSA), *Enterococcus faecalis* (ATCC 29,212, VSE), and *E. coli* (ATCC 25,922). They showed the maximum antibacterial effects against *B. subtilis* with a MIC of 5–10 µg/mL, while they exhibited modest activities towards *Staph. epidermidis* and *Staph. aureus* with MICs of 10–80 µg/mL.

2.8 Antioxidant

The DPPH free radical scavenging assay is widely used for testing antioxidant activity because it changes in coloration from intense violet to bright yellow when reacting with antioxidant compounds [37]. Correspondingly, a higher percentage of scavenging corresponds to a higher antioxidant activity of the isolate being tested. In this study, the crude extract from the PDB culture had a scavenging of 51.5%, which was significantly higher than the PDYB culture (26.4%) (F_2 = 2,299.7; $p < 0.001$). Moreover, the fungal isolates from the PBD culture had the highest antioxidant activity because the DPPH free radical was inactivated in more than 50% after 5 min of reaction (Figure 3). These results suggest that PDB presumably induced a higher synthesis of secondary metabolites responsible for the observed bioactivity.

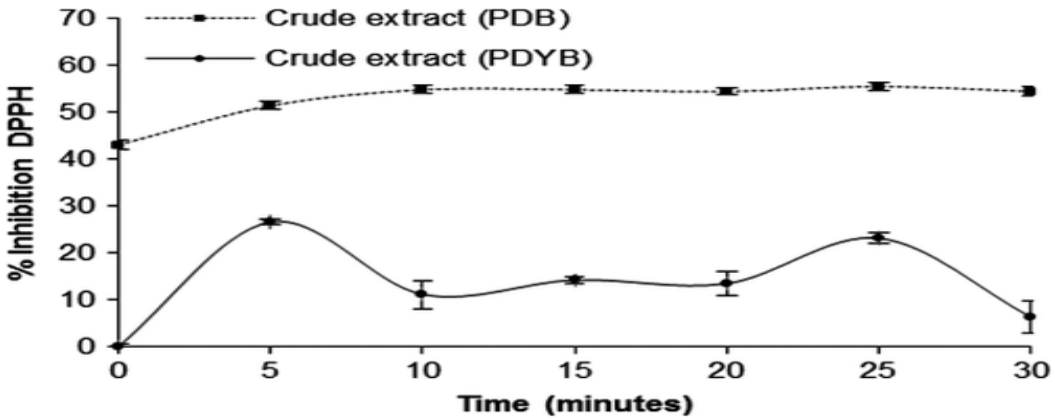


Figure 3: DPPH radical scavenging activity of crude extract obtained from *Fusarium oxysporum* strain EBB-ET-01 growing in potato dextrose broth (PDB) or potato dextrose broth and 0.5% yeast extract (PDYB) at pH 6.0 and 29°C for 30 days

On the other hand, it was impossible to compare the equivalent IC_{50} for gallic acid as DPPH radical inhibitor (0.85 µM) with the same values used for the crude extract, because these contained a no purified mixture of polysaccharides.

Recent studies have shown that endophytic fungi synthesize EPS involved in plant–endophyte interactions and that such biopolymers are characterized by structures that exhibit antioxidant activity [20; 71]. In this study, an endophyte crude extract obtained from the leaves of *Otoba gracilipes* showed a 51.5% of antioxidant activity in 5 min. This is much higher than the 20% scavenging activity of DPPH after 30 min of an EPS obtained from the culture of the strain *Fusarium oxysporum Dzf17* and with a 10-fold lower concentration (200 µg/ml). However, in Li et al., 2011, crude extracts were subjected to deproteination and decolorization processes. Using a different approach by isolating two endophytes (*Aspergillus* sp. y *Fusarium* sp.) from roots of a close relative of *Otoba gracilipes*, a *Virola* sp. tree, and found an EC_{50} of 17.4 µg/ml for antioxidant activity for the crude extracts of *Aspergillus* sp. Such activity was also measured on DPPH and found to be related to the presence of secondary metabolites such as flavonoids. However, no antioxidant activity was detected for crude extracts obtained from *Fusarium* sp. Thus, the high performance of culture media extracts of *Fussarium oxysporium* in this study suggests that the novel fungal strain we describe here has a greater potential for producing exopolysaccharides with antioxidant activity. Given that in our study the fungus was isolated from plant leaves and not from roots, the production of secondary metabolites with antioxidant activity may be tissue-dependent. In addition, it is important to mention that exopolysaccharides with antioxidant activity were

detected as secondary metabolites; therefore, the production of these compounds should be measured at different developmental stages of the fungal endophyte.

Most antioxidants known today are industrially synthesized although being account for causing liver damage and carcinogenesis [143]. In contrast, natural-derived antioxidants, like those produced by endophytes, are not harmful. In particular, due to a high biological diversity and biochemical evolution [34], endophytes can use several substrates, producing a wide array of secondary metabolites [41]. These comprise a large but little-explored proportion of fungal diversity [106; 144]. For example, since the discovery of paclitaxel, a potent anticancer agent isolated from endophytic fungi such as *Taxomyces andreanae* and *Pestalotia* spp., endophytes have been recognized as potential new sources of anticancer, antimicrobial, and antimalarial bioactive metabolites, attracting much more attention from researchers [26]. These metabolites include steroids, xanthines, phenols, isocoumarins, quinones, and terpenoids [119], among others.

It is relevant to mention that the biotechnological use of endophyte metabolites for pharmaceutical or agrochemical products is still in the developmental stage. For example, rugulosin, a mycotoxin produced by a spruce endophyte, has been shown to be effective against pine worm [82], but is still not commercially produced. In this study, we explored secondary metabolites produced by fungal endophytes of *Otoba gracilipes* (family Myristicaceae), a tropical medicinal tree not previously explored for potential bioactive metabolites [12]. Since previous studies have shown that the leaves of other trees such as *Quercus ilex* and *Nothapodytes foetida* contain a high diversity and abundance of fungal endophytic strains [33], we predicted that leaves of *O. gracilipes* would contain a high diversity of endophytic fungi, with a high potential for producing secondary metabolites. For this purpose, we isolated, cultivated, and molecularly characterized a leaf endophyte of *O. gracilipes*. In addition, crude extracts composed mainly of polysaccharides were evaluated for antioxidant activity by a DPPH free radical test.

According to a study by Al-Saleem *et al*. [3], Kojic acid (156) showed a potent antioxidant activity with IC_{50} 33.7 ± 0.8 µg/mL compared to the *P. chrysogenum* extract, which was nearly inactive as revealed by the DPPH free-radical-scavenging technique.

Various antioxidant activity techniques were utilized by Jakovljevic *et al*. [55], including DPPH free-radical-scavenging activity, $Fe2+$-chelating ability, $Fe3+$-reducing power and

total antioxidant activity. *P. chrysogenum* ethanolic extract which was isolated from wastewater, was found to contain higher total phenolic content and better total antioxidant capacity along with ferrous ion chelating ability.

An *et al.* [5], isolated chrysotriazoles A and B (94–95) from *P. chrysogenum* EN118, an endophytic fungus culture extract isolated from the marine brown alga *Sargassum pallidium*. Its radical-scavenging activity was evaluated by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay but did not show any activity.

2.9 Anti-inflammatory

Penicichromanone A (175) and penicichromanone B (176), two novel chroman-4-ones, were isolated by Liu *et al.* (2020) along with three previously identified metabolites, emodin (152), moniliphenone (153), and conioxepinol C (182). These compounds were obtained from an endophytic fungus P. chrysogenum, which was separated from the bark of Eucommia ulmoides Oliver. The anti-inflammatory activity of all the compounds was evaluated using HEK293 cells. The results showed that compounds (175), (152), (153), and (182) had powerful inhibitory actions on TNF-α-stimulated NF-κB activation.

In a previous study conducted by Qi *et al*. [107], five compounds labeled as (40), (41), (43), (48), and (49) were extracted from the fermented cultures of a Huperzia serrata endophytic fungus called P. chrysogenum MT-12. These compounds were found to inhibit the production of nitric oxide in lipopolysaccharide-activated macrophage cells with IC50 values ranging from 4.3–78.2 μM. The standard, indomethacin, had an IC50 value of 33.6 ± 1.4 μM.

Wang *et al*. [137] isolate a new benzoic acid derivative, HPABA (265) from the fermented broth of *P. chrysogenum*., where it presented significant anti-inflammatory with pain killer activities when given at 100 mg/kg, while it showed no ulcerogenic actions.

CONCLUSION

In light of the escalating prevalence of infectious diseases globally, a major concern arises from the growing resistance of microorganisms and viruses to conventional antimicrobial drugs used for both therapeutic and preventive purposes. In response to this pressing challenge, there has been a noteworthy increase in the exploration of natural sources possessing potent antimicrobial properties. Among these, fungi emerge as compelling

candidates within the scientific literature, displaying robust antimicrobial potential against a diverse spectrum, including Gram-positive and Gram-negative bacterial strains, fungal pathogens, and even viruses.

The burgeoning interest in the antimicrobial capabilities of fungi is particularly intriguing in benign drug principle. This sector actively leverages these therapeutic attributes to enhance the quality and effectiveness of its products. A thorough examination of conducted studies highlights the significant presence of substances with substantial antimicrobial activity within for example mushrooms, representative of the fungal kingdom. These bioactive compounds show great promise for various applications, especially in formulating skincare products designed to address persistent skin conditions.

Moreover, the therapeutic potential of these fungal substances extends beyond cosmetics, demonstrating effectiveness in treating various dermatological diseases. This represents a significant step towards integrating natural antimicrobial agents derived from fungi into the complexities of dermatological care.

REFERENCES

1. Agrawal, K. & Verma, P. Fungal Metabolites: A Recent Trend and Its Potential Biotechnological Applications. In New and Future Developments in Microbial Biotechnology and Bioengineering: Recent Advances in Application of Fungi and Fungal Metabolites: Current Aspects; Elsevier: Amsterdam, The Netherlands, 2021; pp. 1–14.
2. Ali, N.A.A., Mothana, R.A.A., Lesnau, A., Pilgrim, H. & Lindequist, U. Antiviral activity of Inonotus hispidus. *Fitoterapia 2003*; 74, 483–485.
3. Al-Saleem, M.S., Hassan, W.H., El Sayed, Z.I., Abdel-Aal, M.M., AbdelMageed, W.M., Abdelsalam, E. & Abdelaziz, S. Metabolic Profiling and in vitro assessment of the biological activities of the ethyl acetate extract of Penicillium chrysogenum "endozoic of Cliona sp. Marine sponge" from the Red Sea (Egypt). *Mar Drugs* 2022; 20:326.
4. Alves, M., Ferreira, I.F.R., Dias, J., Teixeira, V., Martins, A. & Pintado, M. A review on antimicrobial activity of mushroom (Basidiomycetes) extracts and isolated compounds. *Planta. Med.* 2012; 78, 1707–1718.
5. An, C., Li, X., Li, C., Gao, S., Shang, Z. & Wang, B. Triazoles and other n-containing metabolites from the marine-derived Endophytic fungus Penicillium chrysogenum EN-118. *Helv Chim Acta* 2013; 96:682–687.
6. Anke, H., Sterner, O. & Steglich, W. Structure-activity relationships for unsaturated dialdehydes. Mutagenic, antimicrobial, cytotoxic, and phytotoxic activities of merulidial derivatives. *J. Antibiot.* 1989; 42, 738–744.
7. Anke, T., Kupka, J., Schramm, G. & Steglich, W. Antibiotics from Basidiomycetes. X. Scorodonin, a new antibacterial and antifungal metabolite from Marasmius scorodonius (Fr.) Fr. *J. Antibiot.* 1980; 33, 463–467.
8. Aqueveque, P., Becerra, J., Palfner, G., Silva, M., Alarcon, J., Anke, T. & Sterner, O. Antimicrobial activity of metabolites from mycelial cultures of Chilean Basidiomycetes. *J. Chil. Chem. Soc.* 2006; 51, 1057–1060.
9. Barros, L., Baptista, P., Estevinho, L.M. & Ferreira, I.C.F.R. Bioactive properties of the medicinal mushroom Leucopaxillus giganteus mycelium obtained in the presence of different nitrogen sources. *Food Chem.* 2007; 105, 179–186.

10. Beattie, K.D., Rouf, R., Gander, L., May, T.W., Ratkowsky, D., Donner, C.D., Gill, M., Grice, I.D. & Tiralongo, E. Antibacterial metabolites from australian macrofungi from the genus Cortinarius. *Phytochemistry 2010*; 71, 948–955.
11. Bender, S., Dumitrache-Anghel, C.N., Backhaus, J., Christie, G., Cross, R.F., Lonergan, G.T. & Baker, W.L. A case for caution in assessing the antibiotic activity of extracts of culinary-medicinal shiitake mushroom [Lentinus edodes (Berk.) Singer] (Agaricomycetideae). *Int. J. Med. Mushrooms*. 2003; 5, 6.
12. Bernal, H. Y., García, M. H. & Quevedo, S. F. Pautas para el conocimiento, conservación y uso sostenible de las plantas medicinales nativas en Colombia: Estrategia nacional para la conservación de plantas 2011; (p. 230). Bogotá: Instituto de Investigación de Recursos Biológicos Alexander von Humboldt.
13. Bo, G. Giuseppe Brotzu and the discovery of cephalosporins. *Clin. Microbiol. Infect.* 2000; 6, 6–8.
14. Brinch, K.S., Sandberg, A., Baudoux, P., Van Bambeke, F., Tulkens, P.M., Frimodt-Møller, N., Høiby, N., Kristensen, H.H. Plectasin shows intracellular activity against Staphylococcus aureus in Human THP-1 monocytes and in a mouse peritonitis model. *Antimicrob. Agents Chemother.* 2009; 53, 4801–4808.
15. Bush, K. & Bradford, P.A. β-lactams and β-lactamase inhibitors: An overview. Cold Spring Harb. *Perspect. Med.* 2016; 6, a025247.
16. Cardozo, F.T., Camelini, C.M., Mascarello, A., Rossi, M.J., Nunes, R.J. & Barardi, C.R. Antiherpetic activity of a sulfated polysaccharide from Agaricus brasiliensis mycelia. *Antiviral. Res.* 2011; 92, 108–114.
17. Carlet, J. & Mainardi, J.L. Antibacterial agents: back to the future. Can we live with only colistin, co-trimoxazole and fosfomycin? *Clin. Microbiol*. *Infect.* 2012; 18 (1), 1–3.
18. Carlet, J., Rambaud, C. & Pulcini, C. WAAR (World Alliance against Antibiotic Resistance): safeguarding antibiotics. *Antimicrob. Resist. Infect*. *Control*, 2012b; 1 (1), 25–30
19. Chang, A., Sun, S., Li, L., Dai, X., Li, H., He, Q. & Zhu, H. Tyrosol from marine fungi, a novel quorum sensing inhibitor against Chromobacterium violaceum and Pseudomonas aeruginosa. *Bioorg Chem*. 2019; *91*:103140
20. Chen, S., Wang, J., Wang, Z., Lin, X., Zhao, B., Kaliaperumal, K., Liao, X., Tu, Z., Li, J. & Xu, S. Structurally diverse secondary metabolites from a deep-sea-derived fungus Penicillium chrysogenum SCSIO 41001 and their biological evaluation. *Fitoterapia*, 2017; 117:71–78
21. Choudhary, M., Kumar, V., Naik, B., Verma, A., Saris, P.E.J., Kumar, V. & Gupta, S. Antifungal metabolites, their novel sources, and targets to combat drug resistance. *Front. Microbiol.* 2022; 13, 1061603.
22. Clardy, J., Fischbach, M.A. & Currie, C.R. The natural history of antibiotics. *Curr. Biol.* 2009; 19, R437–R441.
23. Coma, V., Deschamps, A. & Martial-Gros, A. Bioactive packaging materials from edible chitosan polymer—Antimicrobial activity assessment on dairy-related contaminants. *J. Food Sci.*2003; 68, 2788–2792.
24. Conrado, R., Gomes, T.C., Roque, G.S.C. & De Souza, A.O. Overview of bioactive fungal secondary metabolites: Cytotoxic and antimicrobial compounds. *Antibiotics 2022*; 11, 1604.
25. Cordes, M.G. Fusidic Acid In *xPharm: The Comprehensive Pharmacology Reference*; Elsevier: Amsterdam, The Netherlands. 2007; pp. 1–4.
26. Cui, J. L., Guo, T. T., Ren, Z. X., Zhang, N. L. & Wang, M. L. Diversity and Antioxidant Activity of Culturable Endophytic Fungi from Alpine Plants of *Rhodiola crenulata*, *R. angusta*, and *R. sachalinensis*. *PLoS ONE*, 2015; 10, 1–16.
27. Develoux, M. Griseofulvin. *Ann. Dermatol. Venereol.* 2001; 128, 1317–1325.
28. Dulger, B., Ergul, C.C. & Gucin, F. Antimicrobial activity of the macrofungus Lepista nuda. *Fitoterapia, 2002*; 73, 695–697.
29. Dutta, B., Lahiri, D., Nag, M., Ghosh, S., Dey, A. & Ray, R.R. Fungi in pharmaceuticals and production of antibiotics. In Applied Mycology: Entrepreneurship with Fungi; *Springer International Publishing: Cham, Germany*, 2022; pp. 233–257.
30. Ershova, E.I., Tikhonova, O.V., Lur'e, L.M., Efremenkova, O.V., Kamzolkina, O.V. & Dudnik, I.V. Antimicrobial activity of Laetiporus sulphureus strains grown in submerged culture. *Antibiot. Khimioter.* 2003; 48, 18–22.
31. Escobar-Paramo, P., Gougat-Barbera, C. & Hochberg, M.E. Evolutionary dynamics of separate and combined exposure of Pseudomonas fluorescens SBW25 to antibiotics and bacteriophage. *Evol. Appl.* 2012; 5 (6), 583–592.

32. Faccin, L.C., Benati, F., Rincão, V.P., Mantovani, M.S., Soares, S.A. & Gonzaga, M.L. Antiviral activity of aqueous and ethanol extracts and of an isolated polysaccharide from Agaricus brasiliensis against poliovirus type 1. *Lett. Appl. Microbiol.* 2007; 45, 24–28.
33. Fathima, S. & Balakrishnan, R. M. Biodiversity, Antimicrobial Potential, and Phylogenetic Placement of an Endophytic Fusarium oxysporum NFX 06 Isolated from Nothapodytes foetida. *Journal of Mycology*, 2013; https://doi.org/10.1155/2013/172056.
34. Fernandes, P. Fusidic Acid: A bacterial elongation factor inhibitor for the oral treatment of acute and chronic staphylococcal infections. *Cold Spring Harb. Perspect. Med.* 2016; 6, a025437.
35. Fernandez, J., Jimenez-Rodriguez, T.W. & Blanca-Lopez, N. Classifying Cephalosporins: From generation to cross-reactivity. *Curr. Opin. Allergy Clin. Immunol.* 2021; 21, 346–354.
36. Galappaththi, M.C.A., Patabendige, N.M., Premarathne, B.M., Hapuarachchi, K.K., Tibpromma, S., Dai, D.Q., Suwannarach, N., Rapior, S. & Karunarathna, S.C. A Review of Ganoderma triterpenoids and their bioactivities. *Biomolecules*. 2022; 13, 24.
37. García, E. J., Oldono, T. L. , Alencar, S. M. , Reis, A. , Loguercio, A. D. & Grande, R. H. Antioxidant activity by DPPH assay of potential solutions to be applied on bleached teeth. *Brazilian Dental Journal*, 2012; 23, 22–27.
38. Gilardoni, G., Clericuzio, M., Tosi, S., Zanoni, G. & Vidari, G. Antifungal acylcyclopentenediones from fruiting bodies of Hygrophorus chrysodon. *J. Nat. Prod.* 2007; 70, 137–139.
39. Goossens, H., Ferech, R., Vander Stichele, R., & Elseviers, M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet.* 2005; *365* (9459), 579–587
40. Gu, C.Q., Li, J. & Chao, F.H. Inhibition of hepatitis B virus by D-fraction from Grifola frondosa: Synergistic effect of combination with interferon-alpha in HepG2 2.2.15. *Antiviral. Res.* 2006; 72, 162–165.
41. Guanatilaka, A. Natural products from plant-associated microorganisms: Distribution, structural diversity, bioactivity, and implications of their occurrence. *Journal of Natural Products*, 2006; 69, 509–526.
42. Guo, Y., Wang, H. & Ng, T.B. Isolation of trichogin, an antifungal protein from fresh fruiting bodies of the edible mushroom Tricholoma giganteum. *Peptide.* 2005; 26, 575–580.
43. Harrison, C.J. & Bratcher, D. Cephalosporins: A review. *Pediatr. Rev.* 2008; 29, 264–273.
44. He, Y., Li, X., Hao, C., Zeng, P., Zhang, M. & Liu, Y. Grifola frondosa polysaccharide: A review of antitumor and other biological activity studies in China. *Discov. Med.* 2018; 25, 159–176.
45. Heim, J., Anke, T., Mocek, U., Steffan, B. & Steglich, W. Antibiotics from Basidiomycetes. XXIX: Pilatin, a new antibiotically active marasmane derivative from cultures of Flagelloscypha pilatii Agerer. *J. Antibiot.*1988; 41, 1752–1757.
46. Hleba, L. Antimicrobial activity of crude methanolic extracts from Ganoderma lucidum and Trametes versicolor. *Anim. Sci. Biotechnol.* 2014; 47, 89–93.
47. Hofle, G. & Oberwinkler, F. The striatins-new antibiotics from the Basidiomycete Cyathus striatus (Huds. Ex Pers.) Willd. *J. Antibiot.* 1977; 977(30), 221–225.
48. Holzknecht, J., Kühbacher, A., Papp, C., Farkas, A., Marcos, J. F., Manzanares, P., Tóth, G. K., Galgóczy, L. & Marx, F. The Penicillium chrysogenum Q176 antimicrobial protein PAFC effectively inhibits the growth of the opportunistic human pathogen Candida albicans. *J Fungi* 2020; 6:141
49. Hosseinnejad, M. & Jafari, S.M. Evaluation of different factors affecting antimicrobial properties of chitosan. *Int. J. Biol. Macromol.* 2016; 85, 467–475.
50. Huber, A., Galgóczy, L., Váradi, G., Holzknecht, J., Kakar, A., Malanovic, N., Leber, R., Koch, J., Keller, M. & Batta, G. Two small, cysteine-rich and cationic antifungal proteins from Penicillium chrysogenum: A comparative study of PAF and PAFB. BBA 2020; 1862:183246
51. Hutchings, M., Truman, A. & Wilkinson, B. Antibiotics: Past, present and future. *Curr. Opin. Microbiol.* 2019; 51, 72–80.
52. Hwang, B.S., Lee, I.K., Choi, H.J. & Yun, B.S. Anti-influenza activities of polyphenols from the medicinal mushroom Phellinus baumii. *Bioorg. Med. Chem. Lett.* 2015; 25, 3256–3260.
53. Isaac, C.E., Jones, A. & Pickard, M.A. Production of cyclosporins by Tylypocladium niveum strains. Antimicrob. *Agents Chemother.* 1990; 34, 121–127.

54. Ishikawa, N.K., Fukushi, Y., Yamaji, K., Tahara, S. & Takahashi, K. Antimicrobial cuparene-type sesquiterpenes, enokipodins c and d, from a mycelial culture of Flammulina velutipes. *J. Nat. Prod.* 2001; 64, 932–934.
55. Jakovljevic, V., Milićević, J., Stojanovic, J., Solujic, A. & Vrvic, M. Antioxidant activity of ethanolic extract of Penicillium chrysogenum and Penicillium fumiculosum. Hemijska Industrija. 2014; https://doi.org/10.2298/HEMIND121102027J
56. Jeihanipour, A., Keikhosro, K. & Taherzadeh, M. Antimicrobial Properties of Fungal Chitosan. *Res. J. Biol. Sci.* 2007; 2, 239–243.
57. Jonsson, M. The Toxicity of Fusarium Mycotoxins Enniatin and Moniliformin; University of Helsinki: Helsinki, Finland, 2017; ISBN 978-952-225-164-0.
58. Kalyoncu, F., Oskay, M., Sa ˘glam, H., Erdo ˘gan, T.F. & Tamer, A.U. Antimicrobial and antioxidant activities of mycelia of 10 wild mushroom species. *J. Med. Food.* 2010; 13, 415–419.
59. Keller, N. P., Turner, G. & Bennett, J. W. F. Ungal secondary metabolism—from biochemistry to genomics. *Nat. Rev. Microbiol.* 2005; 3(12), 937–947
60. Khan, D.A., Banerji, A., Bernstein, J.A., Bilgicer, B., Blumenthal, K., Castells, M., Ein, D., Lang, D.M. & Phillips, E. Cephalosporin allergy: Current understanding and future challenges. *J. Allergy Clin. Immunol. Pract.* 2019; 7, 2105–2114.
61. Klaus, A., Kozarski, M., Vunduk, J., Todorovic, N., Jakovljevic, D., Zizak, Z., Pavlovic, V., Levic, S., Niksic, M. & Van Griensven, L.J.L.D. Biological potential of extracts of the wild edible basidiomycete mushroom Grifola frondosa. *Food Res. Int.* 2015; 67, 272–283.
62. Kohlmünzer, S. Farmakognozja. Podr¸ecznik Dla Studentów Farmacji; Wydawnictwa Lekarskie PZWL: 1998; Warszawa, Poland,
63. Kuklev, D.V., Domb, A.J. & Dembitsky, V.W. Bioactive acetylenic metabolites. *Phytomedicine.* 2013; 20, 1145–1159.
64. Kumar, M. A review of chitin and chitosan applications. *React. Funct. Polym*. 2000; 46, 1–27.
65. Kupka, J., Anke, T., Giannetti, B.M. & Steglich, W. Antibiotics from Basidiomycetes. XIV. Isolation and biological characterization of hypnophilin, pleurotellol, and pleurotellic acid from Pleurotellus hypnophilus (Berk.) Sacc. *Arch. Microbiol.* 1981; 130, 223–227.
66. Larsen, T. O., Smedsgaard, J., Nielsen, K. F., Hansen, M. E. & Frisvad, J. C. Phenotypic taxonomy and metabolite profiling in microbial drug discovery. *Nat. Prod. Rep.* 2005; 22(6), 672–695.
67. Lee, S.J., Yeo, W.H., Yun, B.S. & Yoo, I.D. Isolation and sequence analysis of new peptaibol, boletusin, from Boletus spp. *J. Pept. Sci.* 1999; 5, 374–378.
68. Levy, D., Bluzat, A., Seigneuret, M.; & Rigaud, J.L. Alkali cation transport through liposomes by the antimicrobial fusafungine and its constitutive enniatins. *Biochem. Pharmacol.* 1995; 50, 2105–2107.
69. Li P., Xie D., Chen H., Qiu Y., Zhang X., Zhang S., Wang L., Lin H., Li X. & Liu K. Secondary metabolites from marine-derived fungus Penicillium chrysogenum Y19–1 with proangiogenic and antithrombotic activities. Biochem Syst Ecol. 2023; 107:104625
70. Linnakoski, R., Reshamwala, D., Veteli, P., Cortina-Escribano, M., Vanhanen, H.& Marjomäki, V. Antiviral agents from fungi: Diversity, mechanisms and potential applications. *Front. Microbiol.* 2018; 9, 2325.
71. Liu, X.T., Winkler, A.L., Schwan, W.R., Volk, T.J., Rott, M.A. & Monte, A. Antibacterial Compounds from Mushrooms I: A Lanostane- type triterpene and prenylphenol derivatives from Jahnoporus hirtus and Albatrellus flettii and their activities against Bacillus cereus and Enterococcus faecalis. *Planta. Med.* 2010; 76, 182–185.
72. Long, J., Ji, W., Zhang, D., Zhu, Y. & Bi, Y. Bioactivities and structure-activity relationships of fusidic acid derivatives: A review. Front. Pharmacol. 2021; 12, 759220.
73. Lucia, D. W., Khairunnasa, W. W., Bonifasia, J. A., Dina, C. K., Aris, H., Dodi, N., Lina, K., Arinana, A., Irmanida, B., Djoko, S., Yanti, R., Dikhi, F., Ketut, S. and Decsa, M. H. Antimicrobial activities of fungus comb extracts isolated from Indomalayan termite (Macrotermes gilvus Hagen) mound. *National Center for Biotechnology information.* 2022; 12:14
74. Lund, V.J., Grouin, J.M., Eccles, R., Boucher, C. & Chabolle, F. Efficacy of fusafungine in acute rhinopharyngitis: A pooled analysis. *Rhinology* 2004; 42, 207–212.

75. Luo, D.Q., Shao, H.J., Zhu, H.J. & Liu, J.K. Activity in Vitro and in Vivo against Plant Pathogenic Fungi of Grifolin Isolated from the Basidiomycete Albatrellus Dispansus. Z. Naturforsch. *C. J. Biosci.* 2005; 60, 50–56.
76. Luo, X.J., Li, L.L., Deng, Q.P., Yu, X.F., Yang, L.F., Luo, F.J., Xiao, L.B., Chen, X.Y., Ye, M. & Liu, J.K. Grifolin, a potent antitumour natural product upregulates death-associated protein kinase 1 DAPK1 via P53 in nasopharyngeal carcinoma cells. *Eur. J. Cancer.* 2011; 47, 316–325.
77. Ma, B., Ren, W., Zhou, Y., Ma, J., Ruan, Y. & Wen, C.N. Triterpenoids from the spores of Ganoderma lucidum. *N. Am. J. Med. Sci.* 2011; 3, 495–498.
78. McMorris, T.C. & Turner, W.B. Fungal metabolites. *Mycologia.*1972; 64, 464.
79. Mehta, G. & Murthy, A.S.K. The first total synthesis of the novel triquinane natural products pleurotellol and pleurotellic acid. *Tetrahedron. Lett.* 2003; 44, 5243–5246.
80. Meir, S., Weber, R., Zbinden, R., Ruef, C. & Hasse, B. Extended-spectrum -lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. *Infection.* 2011; 39 (4), 333–340.
81. Midland, S.L., Izac, R.R.;,Wing, R.M., Zaki, A.I., Munnecke, D.E. & Sims, J.J. Melleolide, a new antibiotic from Armillaria mellea. *Tetrahedron. Lett.* 1982; 23, 2515–2518.
82. Miller, E.L. The penicillins: A review and update. *J. Midwifery Womens Health*, 2002; 47, 426–434.
83. Min, B., Kim, S., Oh, Y.L., Kong, W.S., Park, H., Cho, H., Jang, K.Y., Kim, J.G. & Choi, I.G. Genomic discovery of the hyphen gene and biosynthetic pathways for terpenoids in Hypsizygus marmoreus. *BMC Genom.* 2018; *19*, 1–12.
84. Mlinaric, A., Kac, J. & Pohleven, F. Screening of selected wood-damaging fungi for the HIV-1 reverse transcriptase inhibitors. *Acta. Pharm.* 2005; 55, 69–79.
85. Mothana, R.A.A., Jansen, R., Jülich, W.D. & Lindequist, U. Ganomycins A and B, new antimicrobial farnesyl hydroquinones from the Basidiomycete Ganoderma pfeifferi. *J. Nat. Prod.* 2000; 63, 416–418.
86. Muralidhar, R., Gummadi, S.N., Dasu, V.V. & Panda, T. Statistical analysis on some critical parameters affecting the formation of protoplasts from the mycelium of Penicillium griseofulvum. *Biochem. Eng. J.* 2003; 3, 229–235.
87. Mygind, P.H., Fischer, R.L., Schnorr, K.M., Hansen, M.T., Sönksen, C.P., Ludvigsen, S., Raventós, D., Buskov, S., Christensen, B. & De Maria, L. Plectasin is a peptide antibiotic with therapeutic potential from a saprophytic fungus. *Nature.* 2005; 437, 975–980.
88. Nakajima, S., Kawai, K., Yamada, S. & Sawai, Y. Isolation of oospolactone as antifungal principle of Gloeophyllum sepiarium. *Agric. Biol. Chem.* 2014; *40*, 811–812.
89. Nandika, D., Karlinasari, L., Arinana, A., Batubara, I., Sitanggang, P.S., Witasari, S.D., Rachmayanti, Y., Firmansyah, D., Sudiana, I.K. & Hertanto, D.M. Chemical components of fungus comb from Indo-Malayan termite *Macrotermes gilvus* Hagen mound and its bioactivity against wood-staining fungi. *Forests.* 2021; 12,1591. doi: 10.3390/f12111591.
90. Newaz, A.W., Yong, K., Yi, W., Wu, B. & Zhang, Z. (2022). Antimicrobial metabolites from the Indonesian mangrove sediment-derived fungus Penicillium chrysogenum sp. ZZ1151. *Nat Prod Res*. 2022; 37(10):1702–1708
91. Ngai, P.H.K., Zhao, Z. & Ng, T.B. Agrocybin, an antifungal peptide from the edible mushroom Agrocybe cylindracea. *Peptides.* 2005; 26, 191–196.
92. Ngai, P.H.K. & Ng, T.B. A ribonuclease with antimicrobial, antimitogenic and antiproliferative activities from the edible mushroom Pleurotus sajor-caju. *Peptides.* 2004; 25, 11–17.
93. Ninkuu, V., Zhang, L., Yan, J., Fu, Z., Yang, T. & Zeng, H. Biochemistry of terpenes and recent advances in plant protection. *Int. J. Mol. Sci.*2021; 22, 5710.
94. No, H.K., Park, N.Y., Lee, S.H. & Meyers, S.P. Antibacterial activity of chitosans and chitosan oligomers with different molecular weights. *Int. J. Food Microbiol.* 2002; 74, 65–72.
95. Novak, R. & Shlaes, D.M. The pleuromutilin antibiotics: A new class for human use. *Curr Opin Investig Drugs.* 2010; 11, 182–191.
96. Obuchi, T., Kondoh, H., Watanabe, N., Tamai, M., Omura, S., Jun-Shan, Y. & Xiao-Tian, L. Armillaric acid, a new antibiotic produced by Armillaria mellea. *Planta. Med.* 1990; 56, 198–201.

97. Ohta, Y., Lee, J.B., Hayashi, K., Fujita, A., Dong, K.P. & Hayashi, T. In vivo anti-influenza virus activity of an immunomodulatory acidic polysaccharide isolated from Cordyceps militaris grown on germinated soybeans. *J. Agric. Food Chem.* 2007; 55, 10194–10199.
98. Ojala, V., Laitalainen, J. & Jalasvuori, M. Fight evolution with evolution: plasmid-dependent phages with a wide host range prevent the spread of antibiotic resistance. *Evol. Appl.* 2013; 6 (6), 925–932.
99. Oldfield, E. & Feng, X. Resistance-resistant antibiotics. *Trends Pharmacol. Sci.* 2014; 35 (12), 664–674
100. Orfali, R., Perveen, S., AlAjmI, M.F., Ghaffar, S., Rehman, M.T., AlanzI, A.R., Gamea, S.B. & Essa Khwayri, M. Antimicrobial activity of Dihydroisocoumarin isolated from Wadi Lajab sediment-derived fungus Penicillium chrysogenum: in Vitro and silico study. *Molecules.* 2022; 27:3630
101. Ozen, T., Darcan, C., Aktop, O. & Turkekul, I. Screening of antioxidant, antimicrobial activities and chemical contents of edible mushrooms wildly grown in the Black Sea region of Turkey. *Comb. Chem. High Throughput. Screen.* 2011; 14, 72–84.
102. Öztürk, M., Duru, M.E., Kivrak, ¸S., Mercan-Do ˆgan, N., Türkoglu, A. & Özler, M.A. In vitro antioxidant, anticholinesterase and antimicrobial activity studies on three Agaricus species with fatty acid compositions and iron contents: A comparative study on the three most edible mushrooms. *Food Chem.Toxicol.* 2011; 49, 1353–1360.
103. Palmieri, F., Estoppey, A., House, G.L., Lohberger, A., Bindschedler, S., Chain, P.S.G. & Junier, P. Oxalic Acid, a Molecule at the Crossroads of Bacterial-Fungal Interactions. *Adv. Appl. Microbiol.* 2019; 106, 49–77.
104. Paterson, R.R.M. & Ganoderma. A therapeutic fungal biofactory. *Phytochemistry.* 2006; 67, 1985–2001.
105. Peng, J., Zhang, X., Du, L., Wang, W., Zhu, T., Gu, Q. & Li, D. Sorbicatechols A and B, antiviral sorbicillinoids from the marine-derived fungus Penicillium chrysogenum PJX-17. *J Nat Prod.* 2014; 77:424–428
106. Perottoab, S., Angelinic, P., Bianciottob, V., Bonfanteab, P., Girlandaab, M., Kulld, T. & Seloss, M. A. Interactions of fungi with other organisms. *Plant Biosystems-An International Journal Dealing with All Aspects of Plant Biology*, 2013; 147, 208–218. https://doi.org/10.1080/11263504.2012.753136
107. Qi, B., Liu, X., Mo, T., Zhu, Z., Li, J., Wang, J., Shi, X., Zeng, K., Wang, X. & Tu, P. (2017b). 3, 5-Dimethylorsellinic acid-derived meroterpenoids from Penicillium chrysogenum MT-12, an endophytic fungus isolated from Huperzia serrata. *J Nat Prod.* 2017b; 80, 2699–2707
108. Quack, W., Anke, T., Oberwinkler, F., Giannetti, B.M. & Steglich, W. (1978). Antibiotics from Basidiomycetes. V. Merulidial, a new antibiotic from the basidiomycete Merulius tremellosus Fr. *J. Antibiot.* 1978; 31, 737–741.
109. Quang, D.N., Bach, D.D., Hashimoto, T. & Asakawa, Y. Chemical constituents of the vietnamese inedible mushroom Xylaria intracolorata. *Nat. Prod. Res.* 2006; 20, 317–321.
110. Quereshi, S., Pandey, A.K. & Sandhu, S.S. Evaluation of antibacterial activity of different Ganoderma lucidum extracts. PJSR 2010*;* 3, 9–13.
111. Raap, J., Erkelens, K., Ogrel, A., Skladnev, D.A. & Brückner, H. Fungal biosynthesis of non-ribosomal peptide antibiotics and α, α-dialkylated amino acid constituents. *J. Pept. Sci.* 2005; 11, 331–338.
112. Ren, G., Xu, L., Lu, T. & Yin, J. Structural characterization and antiviral activity of lentinan from Lentinus edodes mycelia against infectious hematopoietic necrosis virus. *Int. J. Biol. Macromol.* 2018; 115, 1202–1210.
113. Rosa, L.H., Gomes Machado, K.M., Jacob, C., Capelari, M., Rosa, C.A. & Zani, C.L. Screening of Brazilian Basidiomycetes for antimicrobial activity. Mem. Inst. Oswaldo. *Cruz.* 2003; 98, 967–974.
114. Rossi, C., Eid, M., Rippa, S., Castano, S., Desbat, B., Chopineau, J. & Béven, L. Exploring the membrane mechanism of the bioactive peptaibol ampullosporin a using lipid monolayers and supported biomimetic membranes. *J. Biophys.* 2010; 179641.
115. Sandargo, B., Thongbai, B., Praditya, D., Steinmann, E., Stadler, M. & Surup, F. Antiviral 4-hydroxypleurogrisein and antimicrobial pleurotin derivatives from cultures of the nematophagous Basidiomycete Hohenbuehelia grisea. *Molecules.* 2018; 23, 2697.
116. Sangdee, A., Sangdee, K., Buranrat, B. & Thammawat, S. Effects of mycelial extract and crude protein of the medicinal mushroom, Ophiocordyceps sobolifera, on the pathogenic fungus, Candida albicans. *Trop. Pharm. Res.* 2018; 17, 2449–2454.
117. Savidov, N., Gloriozova, T.A., Poroikov, V.V. & Dembitsky, V.M. Highly oxygenated isoprenoid lipids derived from fungi and fungal endophytes: Origin and biological activities. *Steroids.* 2018; 140, 114–124.

118.Schöfer, H. & Simonsen, L. Fusidic acid in dermatology: An updated review. *Eur. J. Dermatol.* 2010; 20, 006–015.
119.Schulz, B., Boyle, C., Draeger, S., Römmert, A.-K & Krohn, K. Endophytic fungi: A source of novel biologically active secondary metabolites. *Mycological Research*, 2002; 109, 996–1004. https://doi.org/10.1017/S0953756202006342
120.Schwan, W.R., Dunek, C., Gebhardt, M., Engelbrecht, K., Klett, T., Monte, A., Toce, J., Rott, M., Volk, T.J. & LiPuma, J.J. Screening a mushroom extract library for activity against Acinetobacter baumannii and Burkholderia cepacia and the identification of a compound with anti-burkholderia activity. *Ann. Clin. Microbiol. Antimicrob. 2010; 9,* 4.
121.Seo, D.J. & Choi, C. Antiviral bioactive compounds of mushrooms and their antiviral mechanisms: A review. *Viruses.* 2021; 23, 350.
122.Sharma, N., Tapwal, A., Verma, R., Kumar, D.; Nepovimova, E. & Kuca, K. Medicinal, nutritional, and nutraceutical potential of Sparassis Crispa s. lat.: A review. *IMA Fungus.* 2022; 13, 8.
123.Sheena, N., Ajith, T.A., Mathew, A. & Janardhanan, K.K. Antibacterial activity of three macrofungi, Ganoderma lucidum, Navesporus floccosa and Phellinus rimosus occurring in South India. *Pharm. Biol.* 2003; 41, 564–567.
124.Signoretto, C., Burlacchini, G., Marchi, A., Grillenzoni, M., Cavalleri, G., Ciric, L., Lingström, P., Pezzati, E., Daglia, M. & Zaura, E. Testing a low molecular mass fraction of a mushroom (Lentinus edodes) extract formulated as an oral rinse in a cohort of volunteers. *J. Biomed. Biotechnol.*, 2011; 857987.
125.Šiljegovi´c, J.D., Stojkovi´c, D.S., Nikoli´c, M.M., Glamoˇclija, J.M., Sokovi´c, M.D. & ´Ciri´c, A.M. Antimicrobial activity of aqueous extract of Laetiporus sulphureus (Bull.: Fr.) Murill. Zb Matice. *Srp. Print. Nauk*. 2011; 299–305
126.Smania, E.F., Delle Monache, F., Smania, A. & Yunes, R.A. Cuneo, R.S. Antifungal activity of sterols and triterpenes isolated from Ganoderma annulare. *Fitoterapia.* 2003; 74, 375–377.
127.Stärk, A., Anke, T., Mocek, U., Steglich, W., Kirfel, A. & Will, G. Lentinellic acid, a biologically active protoilludane derivative from Lentinellus species (Basidiomycetes). Z Naturforsch. *C J. Biosci.* 1988; 43, 177–183.
128.Steglich, W. & Schramm, G. The strobilurins—New antifungal antibiotics from the Basidiomycete Strobilurus tenacellus. *J. Antibiot.* 1977; 30, 806–810.
129.Sułkowska-Ziaja, K., Trepa, M., Olechowska-Jarząb, A., Nowak, P., Ziaja, M., Kała, K. & Muszyńska, B. Natural Compounds of Fungal Origin with Antimicrobial Activity—Potential Cosmetics Applications. *Pharmaceuticals*, 2023; 16, 1200. https://doi.org/10.3390/ph16091200
130.Sultan, S. The antifungal activity of aqueous and alcoholic extract of mushroom (Agaricus Bisporus) against Aspergillus flavus. In Proceedings of the 1st International Multi-Disciplinary Conference Theme: Sustainable Development and Smart Planning,2020; IMDC-SDSP.
131.Tabuchi, A., Fukushima-Sakuno, E., Osaki-Oka, K., Futamura, Y., Motoyama, T., Osada, H., Ishikawa, N.K., Nagasawa, E. & Tokimoto, K. Productivity and bioactivity of enokipodins A–D of Flammulina rossica and Flammulina velutipes. *Biosci. Biotechnol. Biochem.* 2020; 84, 876–886.
132.Tambekar, D.H., Sonar, T.P., Khodke, M.V. & Khante, B.S. The novel antibacterials from two edible mushrooms: Agaricus bisporus and Pleurotus sajor -caju. *Int. J. Pharmacol.* 2006; 2, 584–587.
133.Tochikura, T.S., Nakashima, H., Hirose, K. & Yamamoto, N. A biological response modifier, PSK, inhibits human immunodeficiency virus infection in vitro. *Biochem. Biophys. Res. Commun.* 1987; 148, 726–733.
134.Tschen, J.S.M., Chen, L.L., Hsieh, S.T. & Wu, T.S. Isolation and phytotoxic effects of helvolic acid from plant pathogenic fungus Sarocladium Oryzae. *Bot. Bull. Acad. Sin.* 1997; 38, 251–256.
135.Turkoglu, A., Duru, M.E., Mercan, N., Kivrak, I. & Gezer, K. Antioxidant and antimicrobial activities of Laetiporus sulphureus (Bull.) Murrill. *Food Chem.* 2006; 101, 267–273.
136.Vlasenko, V.A., Ilyicheva, T.N., Teplyakova, T.V., Svyatchenko, S.V., Asbaganov, S.V. & Zmitrovich, I.V. Antiviral activity of total polysaccharide fraction of water and ethanol extracts of Pleurotus pulmonarius against the influenza A virus. *Curr. Res. Environ. Appl. Mycol.* 2020; 10, 224–235.
137.Wang, H. & Ng, T.B. Eryngin, a novel antifungal peptide from fruiting bodies of the edible mushroom Pleurotus eryngii. *Peptides.* 2004; 25, 1–5.

138.Witasari, L.D., Wahyu, K.W., Anugrahani, B.J., Kurniawan, D.C., Haryanto, A., Nandika, D., Karlinasari, L., Arinana, A., Batubara, I., Santoso, D., Rachmayanti, Y., Firmansyah, D., Sudiana, I.K. & Hertanto, D.M. Antimicrobial activities of fungus comb extracts isolated from Indomalayan termite (Macrotermes gilvus Hagen) mound. *AMB Express.* 2022; 12(1):14. doi: 10.1186/s13568-022-01359-0. PMID: 35142937; PMCID: PMC8831673.

139.Wong, J.H., Ng, T.B., Wang, H., Sze, S.C.W., Zhang, K.Y., Li, Q. & Lu, X. Cordymin, an antifungal peptide from the medicinal fungus Cordyceps militaris. *Phytomedicine.* 2011; 18, 387–392.

140.Yamaç, M. & Bilgili, F. Antimicrobial activities of fruit bodies and/or mycelial cultures of some mushroom isolates. *Pharm. Biol.* 2006; 44, 660–667.

141.Yan, N., He, F., Piraino, F.F., Xiang, H., Chen, J. & Wang, Y. Antiviral activity of a cloned peptide rc28 isolated from the higher basidiomycetes mushroom Rozites caperata in a mouse model of HSV-1 keratitis. *Int. J. Med. Mushrooms.* 2015; 17, 819–828.

142.Yoon, S.Y., Eo, S.K., Kim, Y.S., Lee, C.K. & Han, S.S. Antimicrobial activity of Ganoderma lucidum extract alone and in combination with some antibiotics. *Arch. Pharm. Res.* 1994; 17, 438–442.

143.Yuan, J. F., Zhang, Z. Q., Fan, Z. C. & Yang, J. X. Antioxidant effects and cytotoxicity of three purified polysaccharides from *Ligusticum chuanxiong* Hort. *Carbohydrate Polymers*, 2008; 74, 822–827. https://doi.org/10.1016/j.carbpol.2008.04.040

144.Yuanab, Z., Chena, Y. & Mac, X. Symbiotic fungi in roots of *Artemisia annua* with special reference to endophytic colonizers. *Plant Biosystems-An International Journal Dealing with All Aspects of Plant Biology*, 2011; 145, 495–502.

145. Zhen, X., Gong, T., Wen, Y., Yan, D., Chen, J. & Zhu, P. Chrysoxanthones A-C, three new Xanthone-Chromanone heterodimers from sponge-associated Penicillium chrysogenum HLS111 treated with histone deacetylase inhibitor. *Mar Drugs.*2018; 16,357

Image **Author -1**	Author Name: **Onche Emmanuel (Corresponding Author)** Author Affiliation: Joseph Sarwuan Tarka University, Makurdi Author Address/Institute Address: PMB 2373, Makurdi, Benue State Nigeria.
Image **Author -2**	Author Name: **Ofoegbu Obinna** Author Affiliation: Joseph Sarwuan Tarka University, Makurdi Author Address/Institute Address: PMB 2373, Makurdi, Benue State Nigeria
Image **Author -3**	Author Name: **Ajakaye Oluwadolapo Joy** Author Affiliation: Joseph Sarwuan Tarka University, Makurdi Author Address/Institute Address: PMB 2373, Makurdi, Benue State Nigeria
	Author Name: Lullah-Deh Japheth A.

Image **Author -4**	Author Affiliation Joseph Sarwuan Tarka University, Makurdi Author Address/Institute Address: PMB 2373, Makurdi, Benue State Nigeria
Image **Author -5**	Author Name: Itodo Anthony Author Affiliation: Joseph Sarwuan Tarka University, Makurdi Author Address/Institute Address: PMB 2373, Makurdi, Benue State Nigeria