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Pharmaceuticals from natural products: The utility of the phylogeny

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PHARMACEUTICALS FROM NATURAL PRODUCTS:

THE UTILITY OF THE PHYLOGENY FOR BIOPROSPECTING AND DRUG DISCOVERY

BY

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A MASTER'S THESIS SUBMITTED TO THE FACULTY OF

RICHARD L. CONOLLY COLLEGE, LONG ISLAND UNIVERSITY

IN PARTIAL FULFILLMENT OF REQUIREMENTS

FOR THE DEGREE OF

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AUGUST 2023

MAJOR
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LIFE SCIENCES

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PHARMACEUTICALS FROM NATURAL PRODUCTS:

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ABSTRACT

About 60% of approved drugs during the last 30 years are either directly or indirectly from natural products. Previous studies have shown that the phylogeny has predictive utility in drug discovery. In this study the pharmacological applications of various naturally-derived drugs were mapped on the phylogeny reconstructed from DNA sequences of the source organisms to decipher phylogenetic patterns that may facilitate drug discovery. A multi-step approach was employed starting with a literature search to compile a comprehensive list of pharmaceutical drugs derived from natural sources. A phylogeny was reconstructed from the source organisms and their pharmacological uses mapped on the phylogeny as "traits" based on the organ-system targeted, with the goal of finding clades with a predominant pharmacological application, such that a member within that clade missing such application may be hypothesized to also possess this use/"trait" due to common ancestry. Unexplored taxa belonging to six clades may be good sources of novel pharmaceuticals based on phylogenetic patterns: Kingdoms Bacteria (100%) and Fungi (67%) with many of its investigated taxa with antibiotic effects and therapeutic against infectious diseases; K. Animalia: Subphylum Vertebrata (67%)—for endocrine applications, K. Animalia: Class Ascidiacea (100%)—for oncological applications. K. Plantae: Fabids subgroup (62.5%)—nervous/ psychopharmacological uses, and K. Plantae: Solanaceae family—gastrointestinal uses (50%) as well as nervous applications (67%). These findings underscore the pharmacological utility of the phylogeny shedding light on new avenues for pharmaceutical research and innovation.

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INTRODUCTION

Approximately 60% of all medicines are either natural products or metabolites of natural products (Eddershaw et al., 2000). Plants are a key source of these naturally derived medicines. According to the World Health Organization, approximately 25% of medicines are plant-derived (Sahoo et al., 2010). The number of traditionally used plant species internationally is between 10,000 and 53,000; however, only a limited number have been screened for biological activity (McChesney et al., 2007). Plants with medicinal use are usually found more commonly in some plant families than in others (Moerman et al., 1999). Phylogenetic methods are emerging as tools to discover the plant lineages rich in species with ethnomedicinal use (i.e. those that have metabolites of interest) and hence help predict bioprospecting potential (Saslis-Lagoudakis et al., 2011, 2012; Ernst et al., 2016).

Saslis-Lagoudakis et al. (2012) exemplified the predictive power of traditional medicine in bioprospecting by using phylogenetic data. The researchers reconstructed a genus-level molecular phylogenetic tree representing 20,000 species found in the floras of three disparate biodiversity hotspots: New Zealand, Nepal, and the Cape of South Africa. Borrowing phylogenetic methods from community ecology, they revealed significant clustering of the 1,500 traditionally used species. They also demonstrated shared phylogenetic patterns across the floras, meaning related plants from these regions were used to treat medical conditions in the same therapeutic categories.

Guzman and Molina (2018) also demonstrated the predictive utility of the plant phylogeny, specifically in identifying sources of cardiovascular drugs. Out of 139 plant species in 71 plant families, seven plant families with 45 species emerged as phylogenetically important exhibiting common cardiovascular mechanisms of action within the family. They reported certain plant

families/clades possessing phylogenetically-conserved pharmacological effects. For example, members of Apiaceae (carrot family) promoted diuresis and hypotension; Fabaceae (legumes) species possessed anticoagulant/thrombolytic effects, while members of Zingiberaceae (ginger family) have calcium channel blocking activity.

Prasad et al (2019) also used phylogenetic evidence to determine plant families with antibacterial activity. They demonstrated that seven plant families (Combretaceae, Cupressaceae, Fabaceae, Lamiaceae, Lauraceae, Myrtaceae and Zingiberaceae) showed significant antibacterial activity, with varying mechanisms of action but conserved within the family, and hence are promising leads for the frontiers of antibacterial development.

Plants are not the only naturally derived sources of medications. Fungi have also been used throughout history for their medicinal properties. The earliest known medicinal use of fungi is red yeast rice (made of the yeast *Monascus purpurea*), which was discovered in China around 800 AD (Langdon and Pearce, 2017). Red yeast is the source of Mevastatin, the first statin approved by the United States Food and Drug Administration (FDA) for clinical use for lowering blood cholesterol levels. The second historic and frequently used fungal product is the psilocybin-containing mushrooms, which were used in religious ceremonies by the Aztecs (Díaz, 2017). Psilocybin has been clinically used for anxiety and palliative care (MacReady, 2012).

One of the most groundbreaking discoveries that changed the course of treatment of infectious diseases was a fungus. In 1928, Alexander Fleming, a physician working in London, observed the effect of penicillin, produced by *Penicillium notatum* which was a contaminant growing on a *Staphylococcus* (bacteria)-containing petri dish (Fleming, 1929). Penicillin V was then isolated and became the first true antibiotic. Today, through a variety of medicinal chemistry, hundreds of penicillins have been prepared (Moyer et al.,1946; Barrios-Gonzalez,

1988). Cephalosporins were also discovered from a fungus, *Cephalosporium*, that was isolated from a sewer outlet off the coast of Sardinia in 1948 by Italian scientist Giuseppe Brotzu. Cephalosporin analogues have superior antibacterial activity (Bo, 2000).

Shiitake mushrooms (*Lentinula edodes)*, another fungus, contains lentinan, which is clinically used to boost the immune system and lower cholesterol (Andlauer, 2002). Ergotamine was first isolated in 1918, is a vasoconstricting ergot alkaloid from the fungus *Claviceps purpurea,* used to treat migraines (Graham et al., 1938).

The bacterial and fungal kingdoms have proven to be a source of many therapeutic applications serving as antimicrobial agents, enzyme inhibitors, immunosuppressants, etc (Gupta et al., 2014). Bacteria produce antimicrobial compounds, including bacteriocins, which are ribosomal peptides with a narrow killing spectrum, toxic primarily to closely related bacteria. Bacteriocins, found in various bacterial lineages, have applications in food preservation, safety, and controlling specific bacterial species in food. Lactic acid bacteria and their antimicrobial metabolites, like nisin, are used as natural preservatives in food, with lactobacilli being common probiotics (Gupta et al., 2014).

Enzyme inhibitors from microbial sources have gained attention for their utility in studying enzyme mechanisms and as potential tools in medicine and agriculture (Yuhong et al., 2014). Notable examples include clavulanic acid, which inhibits β-lactamases, and acarbose, an α-glucosidase inhibitor that aids in managing diabetes. Microbial inhibitors like amylase and lipase inhibitors offer potential applications in treating diabetes, obesity, and rumen acidosis (Jayaraj, 2013). Additionally, protease inhibitors from microbial and fungal sources show promise in combatting diseases involving protease activity, such as emphysema and cancer.

Microbial compounds like cyclosporin A, sirolimus (rapamycin), and tacrolimus (FK506) have been discovered as potent immunosuppressants. Cyclosporin A, produced by *Tolypocladium inflatum,* is used in transplants, while sirolimus and tacrolimus, derived from actinomycetes, offer benefits in kidney transplantation and preventing restenosis (Nagano et al., 2006). Tacrolimus has extended applications in various transplants and shows potential for treating conditions like atopic dermatitis and pulmonary fibrosis (Nagano et al., 2006)

Pharmaceutical companies have also explored animals as sources of drugs for modern medical science. A notable example is the development of angiotensin-converting enzyme (ACE) inhibitors from the venom of the snake *Bothrops jararaca*, now widely used to treat high blood pressure (Harvey, 1995). Fish also contribute to medicine, with compounds extracted from them being employed in official treatments and showing promise for anticancer and antiviral drug development (Hamada & Nagai, 1995). Amphibians, e.g. frogs, provide valuable therapeutic compounds, such as peptides from *Phyllomedusa bicolor* used to treat depression, stroke, and Alzheimer's disease (Amato, 1992). Amphibian secretions contain a variety of compounds with pharmacological effects, including defensive, cardiotoxic, myotoxic, and neurotoxic properties, suggesting potential applications in antimicrobial and antifungal treatments (Lazarus & Attila,1993).

In this research study, the utility of pharmacophylogeny to elucidate evolutionarily-conserved pharmacological effects of certain organismal clades based on their clinically-approved therapeutic applications is demonstrated. The naturally derived drugs explored in this study encompass not only the plant phylogeny, which has been extensively studied in the past, but also include animal, bacteria, and fungal sources of drugs. A phylogeny was reconstructed from the source organisms and their pharmacological uses mapped on the

phylogeny as “traits" based on the organ-system targeted, with the goal of finding clades with a predominant pharmacological application, such that a member within that clade missing such application may be hypothesized to also possess this use/“trait” due to common ancestry. This study specifically looked only at naturally derived drugs that are approved for use by regulatory agencies including the US Food & Drug Administration (FDA). The study aims not only to uncover correlations but to forge new pathways in the realm of drug discovery, with the potential to significantly impact medical science and patient care.

MATERIALS AND METHODS

To identify pharmaceutical drugs derived from natural sources, relevant databases such as PubMed and Google Scholar were consulted to compile a total of 106 pharmaceutical drugs derived from natural sources (appendix Table 1). A thorough literature review using keywords and search terms (such as “Naturally derived drugs,” “natural product drug discovery,” “pharmacognosy,” “bioprospecting,” “plant-derived drugs,” “animal-derived drugs,” “microbial drugs,” and “fungal drugs”) related to pharmaceutical drugs derived from plants, animals, bacteria, and fungi was done. Inclusion criteria were established to ensure the selection of relevant pharmaceutical drugs, i.e. drugs approved by the U.S. Food and Drug Administration (FDA) or other international drug agencies (such as National Medical Products Administration - NMPA of China, the Korea Ministry of Food and Drug Safety - KMFD, the Medicines and Healthcare products Regulatory Agency - MHRA of the UK, Pharmaceutical and Medical Devices Agency - PMDA of Japan, and European Medicines Agency - EMA) were considered. Exclusion criteria were defined to exclude drugs that did not meet the study’s objectives. For example, drugs produced using cell cultures were excluded as they are not inherently derived from natural sources. Investigative and experimental drugs were also excluded from the analysis as well as diet/herbal supplements that are not considered “pharmaceutical.” The identified pharmaceutical drugs were cross-referenced to ensure their accuracy and regulatory approval status. This verification was performed by referring to official drug databases (drugbank.com and lexicomp.com) and published literature.

Information was tabulated in an Excel sheet with the following column names: drug name, kingdom, order, family, species, clinically approved use reclassified by body system targeted, and references (Appendix Table 1). To obtain the genetic sequences for each source organism

(genus), a nucleotide BLAST analysis (blastn) on NCBI was performed. Plastid rbcL gene sequences were downloaded for plants, mitochondrial COI sequences for animals, nuclear internal transcribed spacer sequences for fungi, and 16s rDNA sequences for bacteria. These gene sequences were chosen as they have been historically used in phylogenetic reconstruction of each of these groups/kingdoms.

The downloaded FASTA sequences were imported into Geneious (Biomatters, Ltd), and a multiple sequence alignment using MAFFT, (Katoh and Standley, 2013) was performed. After alignment, a phylogenetic tree for each kingdom was generated using the PHYML algorithm (Guindon et al., 2010) in Geneious. The phylogenies were used as input files in Interactive Tree of Life (ITOL), version 2.1 (Letunic & Bork, 2006), an online tool for the display and manipulation of phylogenetic trees. Pharmacological uses were mapped on the phylogeny as "traits" based on the body systems targeted for each source organism, as inferred from the drug's approved therapeutic use.

Mega's Topology Editor (Tamura et al. 2021) was used to merge all the PHYML trees from each kingdom to come up with the final phylogenetic tree (Figure 1). This process allowed for visualizing the relationship between the natural sources of drugs and their corresponding therapeutic indications.

RESULTS

Table 1. Taxonomic grouping, the disease/body systems targeted, and the percentage of genera with the same therapeutic use. Taxa that have no representative sequences in the phylogeny were also added, indicated with (), if they have the same body system application as their relatives. Given that familial diversity was not well represented in other organismal groups except for plants, pharmacophylogenetic patterns above familial level were also highlighted.

Taxon grouping	Disease/Body System Targeted	Number of genera with common disease or body system targeted/Total number of genera in taxon grouping	% Represented
Kingdom Bacteria	Infectious Disease	8/8	100%
Kingdom Fungi	Infectious Disease	4/6	67%
Kingdom Animalia: Subphylum Vertebrata	Endocrine	2/3	67%
Kingdom Animalia: Class Ascidiacea	Oncology	2/2	100%
Kingdom Planta: Clade Fabid	Nervous	4(+1)/7(+1)	62.5%
Kingdom Planta: Family Solanaceae	Gastrointestinal & Nervous	3/6; 4/6, respectively	50%; 67%, respectively

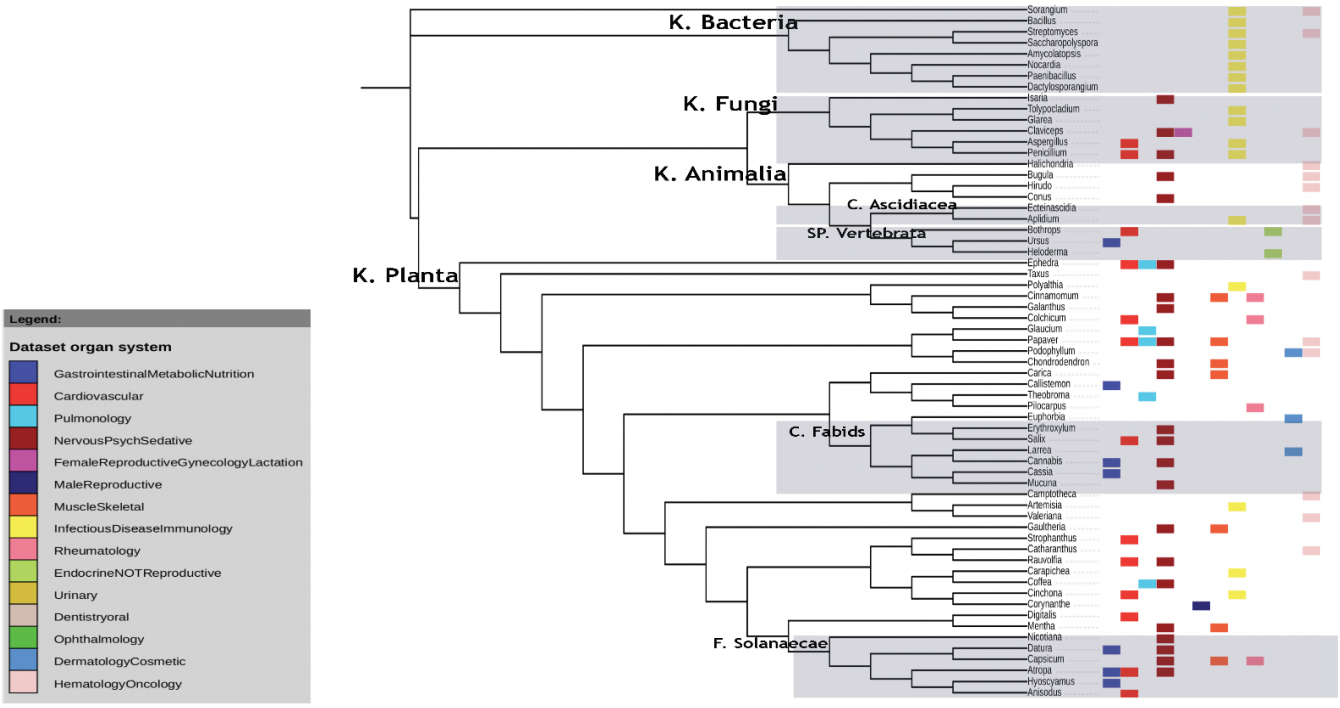

Figure 1. The phylogeny of plant, animal, bacteria, and fungi genera from which clinically approved pharmaceuticals were sourced.

Taxon orders with a majority of the genera sharing a common disease indication or body system target, are labeled and shaded (top to bottom): Kingdom Bacteria (8/8 genera), Kingdom Fungi (4/6 genera), Subphylum Vertebrata (2/3 genera), Class Ascidiacea (2/2 genera), Clade Fabids (5/8 genera), and Family Solanaceae (3/6 genera; 4/6 genera). Disease and body systems indicated are color coded according to the legend (bottom left).

Among the 106 pharmaceutical drugs included in our compilation, 61 were derived from plants, 12 from animals, 21 from bacteria, and 12 from fungi (Appendix Table 1). Given that familial diversity was not well represented in other organismal groups except for plants, pharmacophylogenetic patterns above familial level were also highlighted (Table 1; Fig. 1).

Within the Bacteria kingdom, all eight genera (100%) were linked to pharmaceutical drugs indicated for infectious diseases. Within the Fungi kingdom, four out of six genera (71%) were associated with therapeutic indications for infectious diseases. In the animal kingdom there were two separate groups that were pharmacologically relevant: subphylum Vertebrata, where two out of three genera (67%) demonstrated applications related to the endocrine system. Within class Ascidiacea two out of two genera (100%) demonstrated oncological implications.

The 61 drugs sourced from plants were found to originate from a total of 40 genera, all of which are depicted in the lower section of the phylogenetic tree shown in Figure 1. Within the plant kingdom, two taxonomic orders exhibited correlations with their respective therapeutic uses. Within the Fabids group, four out of seven genera in the phylogenetic tree were associated with neurological uses; the (+1) refers to *Physostigma*, whose sequence was not found in Genbank making it a total of 62.5%. In Solanaceae (nightshade family), three out of six genera (50%) displayed gastrointestinal applications, while another four out of six (67%) exhibited neurological applications (Table 1).

DISCUSSION

The phylogenetic analysis revealed significant correlations between therapeutic indications and six taxonomic groups: Kingdom Bacteria, Kingdom Fungi, two separate clades within Kingdom Animalia (Subphylum Vertebrata and Class Ascidiacea) and two separate clades in Kingdom Plantae (Clade Fabids, and family Solanaceae family).

Kingdom Bacteria and Kingdom Fungi as sources of antibiotics for infectious diseases

As per figure 1, 100% of the genera from the Bacteria Kingdom and 71% of Fungi Kingdom served as sources for pharmaceutical drugs intended to combat infectious diseases. This observation aligns with existing knowledge, as highlighted by Prasad et al. (2019), "antibiotics in current use are derived from a limited number of chemical classes, sourced mostly from bacteria and fungi that were discovered by the 1960s" (Blaskovich et. al 2017). Work by Davies (2006) and Wright (2014) have further emphasized the significance of bacterial secondary metabolites as sources of novel antibiotics. While the prevalence of pharmaceutical drugs sourced from these kingdoms for infectious diseases may not be groundbreaking, it serves to reinforce the established understanding of antibiotic origins and the essential role that bacterial and fungal sources have played in advancing medical treatment options for infectious ailments.

Out of the seven fungal genera, two (*Isaria* and *Claviceps*) did not exhibit clinical antimicrobial applications. Nevertheless, delving into the predictive capacity of phylogenetic analysis, a search for *Isaria* reveals a study conducted by Brel et al. (2020), which identifies *Isaria* farinosa as a source of potentially novel biologically active metabolites displaying strong antibacterial activity. The ability to anticipate such potential from phylogenetic relationships further highlights the valuable role of evolutionary context in predicting biological activities.

The escalating concern of antibiotic resistance presents a challenge to modern medicine. The dwindling efficacy of existing antibiotics against various pathogens emphasizes the urgent need for the development of novel antimicrobial agents. This study brings to light a compelling perspective by emphasizing that these vital new antibiotics could potentially emerge from unexplored taxa within the Bacteria and Fungi Kingdoms. The current landscape of antibiotic resistance is fraught with complex and interrelated issues. Overuse and misuse of antibiotics, coupled with their prolonged exposure to various environments, have contributed to the rise of resistant strains. This relentless evolution of microbial resistance poses a dire threat to public health, as once-treatable infections become increasingly difficult to manage.

By showcasing the potential of untapped sources within the Bacteria and Fungi Kingdoms for antibiotic discovery, this study shows the importance of expanding our exploration into lesser-known taxa. These kingdoms, despite harboring an immense diversity of microorganisms, remain largely unexplored, and their potential contributions to antimicrobial discovery remain untapped. Statistical insights emphasize the vastness of the uncharted terrain. A study by Curtis et al. (2002) highlights the challenges in estimating microbial diversity and the vast extent of uncultured bacterial diversity. Traditionally around 10,000 bacterial species have been described and characterized; however, estimates of total bacterial diversity range from hundreds of thousands to potentially millions of species. Moreover, the study led by Werner et al. (2011) underscores the uniqueness and resilience of bacterial communities in bioenergy systems, showcasing the unexplored diversity in these environments. Torsvik et al. (2002) further delve into prokaryotic diversity, discussing its magnitude, dynamics, and influencing factors, highlighting the vast unknowns in microbial diversity.

Furthermore, the fungal diversity's enigmatic nature is addressed by Hawksworth and Rossman (1997), who discussed the large number of undiscovered fungal species and the difficulties in fungal taxonomy. The number of described fungal species is estimated to be around 120,000; however, the total number of fungal species is thought to be much higher, potentially reaching into millions (Hawksworth, 2012). Blackwell (2011) explores the possibility of millions of undiscovered fungal species, reinforcing the notion of a hidden fungal realm.

Estimates of bacterial and fungal diversity continue to challenge our understanding. According to a report by the World Health Organization (2020), the "Antibacterial Agents in Clinical Development" report, there is a disproportionately low number of antibiotics in development to address the growing threat of drug-resistant infections. This scarcity highlights the inadequacy of our current antibiotic arsenal and highlights the urgent requirement for novel therapeutic options.

In summary, this study underscores the pressing need for novel antibiotics to combat the escalating challenge of antibiotic resistance. The Bacteria and Fungi Kingdoms, with their unexplored diversity, offer a promising avenue for antimicrobial discovery. The existing gaps in our knowledge of microbial diversity and the scarcity of antibiotics in development call for intensified efforts to unearth new sources of therapeutic agents. As we peer into the vast realm of uncharted microorganisms, the potential to find innovative solutions to antibiotic resistance becomes increasingly compelling.

Kingdom Animalia with emphasis on Subphylum Vertebrata and Class Ascidiacea

In subphylum Vertebrata within the animal kingdom, two out of three of genera (*Bothrops* and *Heloderma*) demonstrated applications related to the endocrine system. *Bothrops jararaca*,

the Brazilian pit viper, has been the source of captopril, a widely used medication for managing hypertension, myocardial infarction, and diabetic nephropathy (Bozoghlanian, 2015). Similarly, *Heloderma suspectum,* the Gila monster, has contributed to the development of exenatide (Byetta), a medication employed for the treatment of type 2 diabetes mellitus (Bozoghlanian, 2015).

The utilization of venom and saliva from these vertebrates in the creation of drugs that impact the endocrine system emphasizes the untapped potential of venomous creatures as reservoirs of valuable pharmaceutical compounds. This concept has been supported by research from Fry et al. (2009), which highlights the diverse range of bioactive molecules found within snake venoms, many of which possess therapeutic potential.

Further investigating this finding, we found that there may be more pharmaceutical drugs derived from vertebrates that also have endocrine use suggesting a predictive facet to this phylogenetic approach. For example, Pancrelipase is a drug used for the treatment of pancreatic enzyme deficiency and is derived from porcine pancreatic tissue. Expanding on this notion, the exploration of the *Ursus* genus, the third genus in the phylogenetic tree within subphylum vertebrae (Fig. 1), might yield insights into endocrine applications.

As for the two genera in Class Ascidiacea, also known as sea squirts in the subphylum Tunicata, both *Ecteinascidia* and *Aplidium* exhibit antineoplastic uses (Appendix table 1). While Cragg and Newman (2004) did not specifically mention those genera, the study provides a broader concept for the importance of nature, including marine organisms, as sources of leads for anticancer drug development.

Though not highlighted in the phylogeny because corresponding DNA sequences from Genbank for multiple members were missing, a separate animal clade, Class Demospongiae Isea

sponges), also exhibited antineoplastic use. Within this class, *Halichondria* is a genus on the phylogenetic tree and it is the source of Eribulin, a chemotherapy drug used for the treatment of breast cancer and liposarcoma (McBride et. al, 2012). Another genus of sea sponges, *Tecithethya* (not in the phylogeny due to missing sequence), was found to be a source for two antineoplastic pharmaceuticals, Vidarabine and Cytarabine (Appendix table 1). Moreover, my search unveiled several investigational drugs derived from sea sponges (particularly from the *Negombata* genus and *Discodermia*) that also had anti-cancer implications. As these are investigational drugs, they were excluded. However, their antineoplastic effect speaks to the Demospongiae potential therapeutic significance in the field of oncology and emphasizes the dynamic nature of drug discovery and development wherein investigational medications may eventually contribute to approved treatments and illuminate new directions for therapeutic exploration.

Kingdom Planta with emphasis on Fabids and Family Solanaceae

My analysis of the plant-derived drugs unveils a comprehensive diversity of 40 genera associated with their production. This extensive range resonates with research by Balunas and Kinghorn (2005) and Harvey et al. (2015), who have extensively discussed the chemical diversity found within plant families and the potential of tapping into this diversity for therapeutic discovery. Delving deeper into the plant kingdom, my research reveals correlations between specific taxonomic orders and therapeutic applications.

The Solanaceae family, for instance, exhibits a notable association with both gastrointestinal and neurological treatments. This observation aligns with research by Knapp (2002) and Wink (2008), emphasizing the pharmacological significance of the Solanaceae family, particularly the potential neuroactive properties of certain alkaloids.

Similarly, the Fabids group's connection with neurological uses resonates with a study by Tundis et al. (2013), which has highlighted the presence of neurologically active compounds within this clade. There were certain taxa that were not represented in the phylogeny since they did not have representative sequences in NCBI. For example, *Physostigma* (Fabaceae) which is the source plant for the drug physostigmine, a drug indicated for the reversal of central nervous system anticholinergic syndrome is absent in the phylogeny. Despite its absence in the phylogenetic tree, like other Fabids, it has neurological uses.

The findings from the phylogenetic analysis served as a basis for identifying potential new sources of pharmaceutical drugs. However, experimental validation and further investigations, such as chemical profiling and bioactivity assays, are essential to confirm the presence of bioactive compounds and evaluate their potential therapeutic applications. Additionally, the exploration of additional datasets and incorporation of more genera may be considered in future studies to expand the scope of the analysis and enhance the identification of novel pharmaceutical drug sources.

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APPENDIX

Table 1.2 Pharmaceutical drugs used in this study. List of drugs with natural sources with the following column names: Drug name, Kingdom, Order, Family, Species, clinically approved use reclassified by body system targeted, and References.

Drug	Kingdom	Order	Family	Species	Dz/ condition indicated for	System	References
Anisodamine (Approved in China)	Plants	Solanales/ Polemoniales	Solanaceae	Anisodus tanguticus	Antispasmodic/ anticholinergic: Tx of acute circulatory shock	Cardio, GI	Zhang et al., 2023
Artemether-lumefantrine	Plants	Asterales	Asteraceae	Artemisia annua	Antimalarial	Infectious	Premji, 2009
Artemisinin	Plants	Asterales	Asteraceae	Artemisia annua	Antimalarial	Infectious	Premji, 2009
Atropine	Plants	Solanales/ Polemoniales	Solanaceae	Atropa belladonna	Bradycardia during neuromuscular blockade reversal; Inhibition of salivation and secretions (preanesthesia); reduce diarrhea; Muscarine-containing mushroom poisoning; Organophosphate or carbamate insecticide or nerve agent poisoning	Cardio; GI; Neuro	Lee, 2007
Nitisinone	Plants	Myrtales	Myrtales	Callistemon citrinus	Hereditary tyrosinemia type 1	Metabolic/ Genetic	Veeresham 2012
Irinotecan	Plants	Cornales	Nyssaceae	Camptotheca acuminata	Colorectal cancer, metastatic	Onco	Efferth 2007
Belotecan (Approved in South Korea)	Plants	Cornales	Nyssaceae	Camptotheca acuminata	Ovarian cancer, and small cell lung cancer	Onco	Efferth 2007
Trastuzumab deruxtecan	Plants	Cornales	Nyssaceae	Camptotheca acuminata	Breast cancer, gastric cancer, and non-small cell lung carcinoma	Onco	Efferth 2007
Topotecan	Plants	Cornales	Nyssaceae	Camptotheca acuminata	Ovarian, cervical cancer, and small cell lung carcinoma	Onco	Li et al., 2005
Dronabinol	Plants	Rosales	Cannabaceae	Cannabis sativa	Refractory nausea (in HIV/ AIDS; Chemotherapy-induced)	GI	Veeresham, 2012
Cannabidiol	Plants	Rosales	Cannabaceae	Cannabis sativa	Used for seizure disorders (epilepsy) and other neurodegenerative disorders	Neuro	Devinsky, 2014

Capsaicin	Plants	Solanales	Solanaceae	Capsicum annuum	Muscle/Joint pain; Neuropathic pain (8% patch): associated with postherpetic neuralgia and diabetic peripheral neuropathy of the feet in adults. - used to help relieve a certain type of pain known as neuralgia	Rheum; MSK; Neuro	Fattori, 2016
Emetine	Plants	Gentianales	Rubiaceae	Carapichea ipecacuanha	Amebiasis	Infectious	de Oliveira, 2010
Chymopapain	Plants	Brassicales	Caricaceae	Carica papaya	For the development of chemonucleolysis which is used for the digestion of the nucleus pulposus in patients with disc herniation confirmed by myelography	Neuro, Musculoskeletal	Vij et al., 2015
Senna	Plants	Fabales	Fabaceae	Cassia fistula	Laxative	GI	Akanmu et al., 2004
Vincristine/ Vinblastin	Plants	Gentianales	Apocynaceae	Catharanthus roseus	Antineoplastic agent used against nephroblastoma,non-Hodgkin's lymphoma and as an immunosuppressant	Onco	Qu et al., 2018
Tubocurarine - (FDA Approved but Discontinued)	Plants	Ranunculales	Menispermaceae	Chondrodendron tomentosum	Used as an anesthetic to provide skeletal muscle relaxation during surgery or mechanical ventilation and also as a diagnosis agent for myasthenia gravis.	Neuro; Musculoskeletal	Du et al., 2018
Quinidine	Plants	Gentianales	Rubiaceae	Cinchona ledgeriana	Atrial fibrillation/flutter, Paroxysmal atrial fibrillation/flutter, Ventricular arrhythmias	Cardio	Anderson et al., 1982
Quinine	Plants	Gentianales	Rubiaceae	Cinchona officinalis	Malaria and babesiosis	Infectious	Anderson et al., 1982
Camphor	Plants	Laurales	Lauraceae	Cinnamomum camphora	Antitussive, relief for minor muscle and joint aches and pains associated with arthritis, simple backache, muscle sprains and strains, and bruises, benadryl anti-itch gel.	Neuro, Allergy, Musculoskeletal, Rheum	Mishra & Dwivedi, 2021

Caffeine	Plants	Gentianales	Rubiaceae	Coffea canephora	Different respiratory disorders, used as a psychoactive agent to enhance cognitive function, improve muscle endurances, concentration and wakefulness and relieves fatigue.	Resp, Neuro/ Psych	Wale et al., 2023
Colchicine	Plants	Liliales	Colchicaceae	Colchicum autumnale	Gout flares, Stable ischemic heart disease, prevention of atherosclerotic cardiovascular events	Rheumatology, Cardio	Karamanou, et al. 2018
Demecolcine	Plants	Liliales	Colchicaceae	Colchicum autumnale	Reduces side effects of radiation; prevention of atherosclerotic cardiovascular events	Onco; Cardio	Bass et al., 2019
Yohimbine	Plants	Gentianales	Rubiaceae	Corynanthe johimbe	Erectile Dysfunction via increasing peripheral blood flow	Male Repro	Du et al., 2018
Scopolamine	Plants	Solanales	Solanaceae	Datura inoxia	Gastrointestinal/genitourinary spasm; Motion sickness prevention; Postoperative nausea and/or vomiting prevention	GI, Neuro	Shi et al., 2022
Acetyldigoxin	Plants	Lamiales	Plantaginaceae	Digitalis lanata	Congestive heart failure, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, and cardiogenic shock	Cardio	Moore & Taylor, 1996
Deslanoside	Plants	Lamiales	Plantaginaceae	Digitalis lanata	Congestive cardiac insufficiency, arrhythmias and heart failure.	Cardio	Pandey et al., 2017
Digitoxin	Plants	Lamiales	Plantaginaceae	Digitalis lanata	Congestive heart failure, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, and cardiogenic shock	Cardio	Moore & Taylor, 1996
Ephedrine	Plants	Ephedrales	Ephedraceae	Ephedra sinica	Low blood pressure and narcolepsy, and act as bronchodilators to treat asthma, used in anesthsia may decrease motion sickness.	Cardio, Resp, Neuro	Gurley, et al., 1998
Cocaine	Plants	Malpighiales	Erythroxylaceae	Erythroxylum coca	Local (topical) anesthesia of accessible mucous membranes of the oral, laryngeal and nasal cavities	Neuro/ Psych	Hahn et al., 2001
ingenol mebutate (picato)	Plants	Malpighiales	Euphorbiaceae	Euphorbia peplus	Actinic keratosis on face, trunk and extremities.	Derm	Gras, 2013

FDA approved but Discontinued							
galantamine	Plants	Asparagales	Amaryllidaceae	Galanthus nivalis	Cognitive decline in mild to moderate Alzheimer's disease and various other memory impairments.	Neuro/ Psych	Kim et al., 2017
Methyl salicylate	Plants	Ericales	Ericaceae	Gaultheria procumbens	Pain relief: Temporary relief of minor aches and pains of muscle and joints associated with arthritis, bruises, simple backache, cramps, sprains, and strains.	Neuro, Musculoskeletal	Ribnicky et al., 2003
Glaucine Approved in Eastern Europe, Iceland	Plants	Ranunculales	Papaveraceae	Glaucium flavum	Antitussive	Pulm	Gastpar, 1984
Hyoscyamine	Plants	Solanales/ Polemoniales	Solanaceae	Hyoscyamus niger	Gastrointestinal disorders	GI	Al-Snafi, 2018
Masoprocol	Plants	Zygophyllales	Zygophyllaceae	Larrea divaricata	Actinic keratoses before becoming cancerous	Derm	Olsen et al., 1991
Menthol (Levomenthol)	Plants	Lamiales	Lamiaceae	Mentha piperita	Anesthetic: relief of pain, itching, relief of mild to moderate muscle and joint pain	Neuro, Musculoskeletal	Galeotti, et al., 2001
Levodopa	Plants	Fabales	Fabaceae	Mucuna pruriens	Anti-parkinsons	Neuro/ Psych	Cilia, et al. 2017
Nicotine	Plants	Solanales/ Polemoniales	Solanaceae	Nicotiana tabacum	Smoking cessation Aid	Neuro/ Psych	Kishore, 2014
Noscapine	Plants	Ranunculales	Papaveraceae	Papaver somniferum	Mild analgesic, antitussive, and potential antineoplastic activities.	Neuro; onco, resp	Winzer, et al., 2012
Diacetylmorphine	Plants	Papaverales	Papaveraceae	Papaver somniferum	Opioid use disorder, maintenance treatment	Neuro/ Psych	Gutstein et al., 2006
Morphine	Plants	Papaverales	Papaveraceae	Papaver somniferum	Pain management, acute and chronic pain	Neuro/ Psych	Gutstein et al., 2006
Apomorphine	Plants	Papaverales	Papaveraceae	Papaver somniferum	Advanced parkinson's disease (muscle stiffness, loss of muscle control).	Neuro, Musculoskeletal	Kempster et al., 2002
codeine	Plants	Papaverales	Papaveraceae	Papaver somniferum	Mild to moderate pain and to relieve coughing, pain management.	Neuro/ Psych, Pulm	Chen et al., 2022

papaverine	Plants	Ranunculales	Papaveraceae	Papaver somniferum	Vasodilator: for various vascular spasms associated with smooth muscle spasms as in myocardial infarction, angina, peripheral and pulmonary embolism, peripheral vascular disease; cerebral angiospastic states; visceral spasms (ureteral, biliary, and GI colic)	Cardio	Ashrafi et al., 2023
Physostigmine	Plants	Fabales	Fabaceae	Physostigma venenosum	Reversal of central nervous system anticholinergic syndrome	Neuro	Batiha et al., 2020
Pilocarpine	Plants	Sapindales	Rutaceae	Pilocarpus jaborandi	Systemic: Xerostomia caused by radiotherapy for head and neck cancers and patients with Sjögren syndrome. Ophthalmic: Chronic open-angle glaucoma and Acute angle-closure glaucoma	Rheumatology	De Abreu et al. 2005
Etoposide	Plants	Ranunculales	Berberidaceae	Podophyllum peltatum	Small cell lung cancer (oral and IV) and testicular cancer	Onco	Kluska et al., 2021
Podofilox	Plants	Ranunculales	Berberidaceae	Podophyllum peltatum	Keratolytic Agent: Tx of Genital and perianal warts	Derm	Shultz et al., 2021
Teniposide	Plants	Ranunculales	Berberidaceae	Podophyllum peltatum	Acute lymphoblastic leukemia, refractory	Onco	Moraes et al. 2021
Benzyl benzoate	Plants	Magnoliales	Annonaceae	Polyalthia longifolia	Scabies, topical tx for pediculosis	Infectious	Maury et al., 2012
Deserpidine	Plants	Gentianales	Apocynaceae	Rauvolfia canescens	Antihypertensive	Cardio	Schneider et al., 1955
Ajmalicine/ ajmaline	Plants	Gentianales	Apocynaceae	Rauvolfia serpentina	Antiarrhythmic used to manage a variety of forms of tachycardias	Cardio	Singh 2017
Rescinnamine	Plants	Gentianales	Apocynaceae	Rauvolfia serpentina	Hypertension	Cardio	Kumari, et al., 2013
reserpine	Plants	Gentianales	Apocynaceae	Rauvolfia serpentina	Antihypertensive agent to treat high blood pressure, also used as tranquilizer and antipsychotic agent.	Cardio, Neuro/ Psych	Jerie, 2007

Acetylsalicylic Acid (Aspirin)	Plants	Malpighiales	Salicaceae	Salix alba L.	Analgesic: Inflammation, Pain, Osteoarthritis Vascular indications including ischemic stroke, transient ischemic attack, acute coronary syndromes, secondary prevention after acute coronary syndromes, and management of stable ischemic heart; revascularization procedures	Neuro; Cardio	Gyawali, 2013
Ouabain	Plants	Gentianales	Apocynaceae	Strophanthus gratus	Atrial fibrillation and flutter and heart failure	Cardio	Shah 2017
Docetaxel	Plants	Pinales	Taxaceae	Taxus brevifolia	Breast, gastric adenocarcinoma, head and neck cancer, non-small lung cancer, prostate cancer	Onco	Mamadalieva et al., 2020
Paclitaxel	Plants	Pinales	Taxaceae	Taxus brevifolia	Breast, lung, and ovarian cancer, as well as Kaposi's sarcoma.	Onco	Mamadalieva et al., 2020
theophylline	Plants	Malvales	Malvaceae	Theobroma cacao	Asthma and chronic obstructive pulmonary disease (COPD)	Pulm	Lo Coco et al., 2007
Valerate	Plants	Dipsacales	Valerianaceae	Valeriana wallichii	Antitumor activity	Onco	Nandhini et al., 2018
plitidepsin	Animals	Enterogona	Polyclinidae	Aplidium albicans	Tumors, and as antiviral and immunosuppressive agent.	Infectious; Onco	Leisch et al., 2019
Captopril	Animal	Squamata	Viperidae	Bothrops jararaca	Anti-hypertensive, protective properties in congestive heart failure, post-myocardial infarction, and treatment of diabetic nephropathy in patients with type 1 insulin-dependent diabetes mellitus and retinopathy.	Cardio, Endo	Bozoghlanian 2015
Bryostatin I	Animals	Cheilostomata	Bugulidae	Bugula neritina	Antitumor/ antineoplastic activity and synergistic chemotheoreputic activity, immunity, cognition and memory enhancement and improve alzheimer's disease.; FDA orphan drug designation for Fragile X syndrome	Onco; Neuro	Pettit et al., 1984
Ziconotide	Animals	Sorbeoconcha	Conidae	Conus magus	Analgesic to treat severe chronic pain.	Neuro/ Psych	Miljanich 2004

Trabectedin	Animal	Enterogona	Perophoridae	Ecteinascidia turbinata	Antineoplastic: Used for treating tumors (ovarian cancer, soft tissue) Sarcinoma)	Onco	Larsen, 2016
Eribulin (Halichondrin B analog)	Animals	Suberitida	Halichondriidae	Halichondria okadai	Antineoplastic agent	Onco	McBride et al., 2012
Exenatide (Byetta)	Animal	Squamata	Helodermatidae	Heloderma suspectum	Diabetes mellitus	Endo	Bozoghlanian 2015
Lepirudin FDA Approved but withdrawn	Animal	Hirudinida	Hirudinidae	Hirudo medicinali	Anti-coagulant; Direct thrombin inhibitor; in patients with heparin-induced thrombocytopenia	Hematological	Bozoghlanian 2015
Eptifibatide (Integrilin)	Animal	Squamata	Viperidae	Sistrurus miliarius barbouri	Acute coronary syndromes, usually at the time of Percutaneous Coronary Intervention, and usually in combination with aspirin and heparin	Hematological, cardio	Bozoghlanian 2015
Vidarabine	Animals	Tethyidae	Tethyidae	Tectitethya crypta	Used as Antiviral agent and for the treatment of severe acute respiratory syndrome (SARS). Later on used for the synthesis of potent anticancer agent	Infectious Disease, Resp, Onco	Florean et al., 2022
Cytarabine	Animal	Tethyida	Tethyidae	Tectitethya crypta	Antineoplastic agent: AML, APML, ALL, CML, CLL, primary CNS lymphomas, Hodgkin and non-Hodgkin lymphomas	Onco	Bozoghlanian 2015
Ursodiol	Animal	Carnivora	Ursidae	Ursus species (from liver)	Gallstone dissolution agent: Cholelithiasis, conditions causing cholestasis, including primary biliary cirrhosis	GI	Bozoghlanian 2015
Augmentin (Amoxicillin)	Bacteria	Actinomycetales	Actinomycetaceae	Actinomyces species	Susceptible bacterial infections of the ear, nose, throat, genitourinary tract, skin, skin structure, and lower respiratory tract	Infectious Disease	Strohl 2003
Vancomycin	Bacteria	Actinomycetales	Pseudonocardiaceae	Amycolatopsis orientalis	Against different gram positive strains of Bacteria	Infectious Disease	Nagarajan 1991
Rifamycins	Bacteria	Actinomycetales	Pseudonocardiaceae	Amycolatopsis rifamycinica	Travelers' diarrhea (TD) caused by noninvasive strains of Escherichia coli in adults	Infectious Disease	Bala et al., 2004

Bacitracin	Bacteria	Bacillales	Bacillacea e	Bacillus licheniformis	To prevent wound infections, treat pneumonia and empyema in infants, and to treat skin and eye infections.	Infectious Disease	Jin et al., 2021
Fidaxomicin	Bacteria	Actinomyce tales	Micromon osporaceae	Dactylosporangiu m aurantiacum	Antibacterial agent used to treat different infections mainly against Clostridium difficile infection	Infectious Disease	Hardesty et al., 2011
Nocardicin A (Approved in Japan)	Bacteria	Actinomyce tales	Nocardiac eae	Nocardia uniformis	Bacterial Infections	Infectious Disease	Hosoda et al., 1977
Polymyxin B	Bacteria	Bacillales	Paenibacill aceae	Paenibacillus polymyxa	Infections of the urinary tract, meninges, and blood stream, caused by susceptible strains of Pseudomonas aeruginosa	Infectious Disease	Shaheen et al., 2011
Erythromycin	Bacteria	Actinomyce tales	Pseudonoc ardiaceae	Saccharopolyspor a erythraea (Streptomyces erythraeus)	Anti bacterial or anti infective	Infectious Disease	Chng et al., 2008
Ixabepilone	Bacteria	Myxococcal es	Polyangiac eae	Sorangium cellulosum	Metastatic or locally advanced breast cancer that is resistant or refractory to anthracyclines, taxanes, and capecitabine.	Onco	Lee et al., 2008
ivermectin	Bacteria	Actinomyce tales	Streptomy cetaceae	Streptomyces avermitilis	Anthelmintics to treat parasitic worms and insect pests.	Infectious Disease	Ikeda 2003
Amrubicin (Approved in Japan)	Bacteria	Actinomyce tales	Streptomy cetaceae	Streptomyces bacterium	Lung cancer	Onco	Chang et al., 2011
Imipenem	Bacteria	Actinomyce tales	Streptomy cetaceae	Streptomyces cattleya	Anti-bacterial	Infectious Disease	Geddes et al., 1985
Streptomycin	Bacteria	Actinomyce tales	Streptomy cetaceae	Streptomyces griseus	Tuberculosis and other infections	Infectious Disease	Ohnishi et al., 2008
Candicidin	Bacteria	Actinomyce tales	Streptomy cetaceae	Streptomyces griseus	Fungal infections such as vulvovaginal candidiasis.	Infectious Disease	Gil et al., 2003
Aztreonam	Bacteria	Actinomyce tales	Streptomy cetaceae	Streptomyces lactamdurans	Anti bacterial or anti infective and antifungal activity	Infectious Disease	Vilvanathan 2021
Amphotericin B	Bacteria	Actinomyce tales	Streptomy cetaceae	Streptomyces nodosus	Antifungal used to treat fungal infections in neutropenic patients, cryptococcal meningitis in HIV infection, fungal infections, and leishmaniasis	Infectious Disease	Ellis 2002

Doxorubicin	Bacteria	Actinomycetales	Actinomycetaceae or Streptomycetaceae	Streptomyces peucetius	Breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia	Onco	Malla et al., 2010
oxytetracycline	Bacteria	Actinomycetales	Streptomycetaceae	Streptomyces rimosus	Antibacterial	Infectious Disease	Petković et al., 2017
Daptomycin	Bacteria	Actinomycetales	Streptomycetaceae	Streptomyces roseosporus.	Complicated skin and skin structure infections (cSSSI) in patients one year of age and older. It is also indicated for the treatment of Staphylococcus aureus bloodstream infections (bacteremia)	Infectious Disease	Ye et al., 2019
Chloramphenicol	Bacteria	Actinomycetales	Streptomycetaceae	Streptomyces venezuelae	Antibiotic	Infectious Disease	Hanekamp et al., 2015
Bleomycin	Bacteria	Actinomycetales	Streptomycetaceae	Streptomyces verticillus	Head and neck cancers; Hodgkin lymphoma; Malignant pleural effusion; Testicular cancer	Onco	Sánchez et al., 2001
Lovastatin	Fungi	Eurotiales	Trichocomaceae	Aspergillus terreus	Dyslipidemia, hypercholesterolemia and the prevention of cardiovascular disease.	Cardio	Bhargavi et al., 2014
Itraconazole	Fungi	Eurotiales	Trichocomaceae	Aspergillus terreus	Fungal infections in the lungs that can spread throughout the body. Itraconazole capsules (Sporanox) are also used to treat fungal infections of the fingernails and toenails	Infectious disease	Goldberg et al., 1993
Ergotamine	Fungi	Hypocreales	Clavicipitaceae	Claviceps purpurea	Migraines	Neuro/ Psych	Eadie 2004
Ergometrine	Fungi	Hypocreales	Clavicipitaceae	claviceps purpurea	Postpartum and postabortion hemorrhage caused by uterine atony	OBGYN, Hematology	Van Dongen 1995
Fusidic Acid (not US approved but used worldwide elsewhere)	Fungi	Hypocreales	Nectriaceae	Fusidium coccineum	Skin infections and Ophthalmic infections/conjunctivitis	Infectious Disease	Dobie et al., 2004
Caspofungin	Fungus	Leotiales	Helotiaceae	Glarea lozoyensis	Esophageal candidiasis and invasive aspergillosis	Infectious Disease	Balkovec et al., 2014
Fingolimod	Fungi	Hypocreales	Clavicipitaceae	Isaria sinclairii	Multiple Sclerosis	Neuro/ Psych	Strader et al, 2011
penicillin	Fungi	Eurotiales	Trichocomaceae	Penicillium chrysogenum	Bacterial Infections	Infectious Disease	Müller et al., 1991

Pravastatin/ Pravachol	Fungi	Eurotiales	Trichocomaceae	Penicillium compactum	Hypercholesterolemia, and atherosclerotic cardiovascular disease	Cardio	Langdon et al., 2017
Griseofulvin	Fungi	Eurotiales	Trichocomaceae	Penicillium griseofulvum	Dermatophyte infections: Used as antifungal to treat Microsporum scalp infections and orally only for dermatophytosis.	Infectious Disease	Jumiati et al., 2021
Mycophenolic acid	Fungi	Eurotiales	Trichocomaceae	Penicillium stoloniferum	Immunosuppressant: Prophylaxis of organ rejection in patients receiving allogeneic renal, mycophenolate sodium, delayed release, cardiac, or liver (mycophenolate mofetil) transplants, in combination with other immunosuppressants.	Immunology	Detroy et al., 1973
cyclosporine	Fungi	Hypocreales	Ophiocordycipitaceae	Tolypocladium inflatum	Graft-versus-host disease in bone marrow transplantation and to prevent rejection of kidney, heart, and liver transplants, also to treat rheumatoid arthritis and psoriasis, persistent nummular keratitis following adenoviral keratoconjunctivitis.	Immunology	Yang et al., 2019