MINI-REVIEW

Impact of novel microbial secondary metabolites on the pharma industry

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Abstract

Microorganisms are remarkable producers of a wide diversity of natural products that significantly improve human health and well-being. Currently, these natural products comprise half of all the pharmaceuticals on the market. After the discovery of penicillin by Alexander Fleming 85 years ago, the search for and study of antibiotics began to gain relevance as drugs. Since then, antibiotics have played a valuable role in treating infectious diseases and have saved many human lives. New molecules with anticancer, hypocholesterolemic, and immunosuppressive activity have now been introduced to treat other relevant diseases. Smaller biotechnology companies and academic laboratories generate novel antibiotics and other secondary metabolites that big pharmaceutical companies no longer develop. The purpose of this review is to illustrate some of the recent developments and to show the potential that some modern technologies like metagenomics and genome mining offer for the discovery and development of new molecules, with different functions like therapeutic alternatives needed to overcome current severe problems, such as the SARS-CoV-2 pandemic, antibiotic resistance, and other emerging diseases.

Key points

● *Novel alternatives for the treatment of infections caused by bacteria, fungi, and viruses.*
● *Second wave of efforts of microbial origin against SARS-CoV-2 and related variants.*
● *Microbial drugs used in clinical practice as hypocholesterolemic agents, immunosuppressants, and anticancer therapy.*

Keywords Microbial natural products · Antibiotics · Hypocholesterolemics · Anticancer drugs · Immunosuppressants · Antibiotic resistance

Abbreviations

FDA	Food and Drug Administration
NA	Not applicable
cSSSI	Complicated skin, and skin structure infections
ABSSSIs	Acute bacterial skin, and skin structure infections
cUTI	Complicated urinary tract infections
cIAI	Complicated intra-abdominal infections
HABP/VABP	Hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia
CABP	Community-acquired bacterial pneumonia. Estimate of U.S. Sales for 2018 was based on data previously reported Carr and Stringer 2019

This review is dedicated to the memory of Prof. Arnold L. Demain, who passed away while this paper was being written.

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Introduction

Microbes have provided us with thousands of valuable natural drugs with novel structures and bioactivities (Pham et al. 2019). Microbes produce around 22,500 biologically active compounds; 45% come from actinobacteria, 38% from fungi, and 17% via unicellular

bacteria (Berdy 2015). Thus, the microbial role in producing antibiotics and other drugs for non-infectious diseases has been spectacular. Besides, chemical modification has raised these structures to drugs with new attractive properties. Today, over 200,000 different secondary metabolite structures are known (Ruchika et al. 2019). Drugs of microbial origin (MPs) can be classified as (i) original MPs, (ii) products derived or chemically synthesized from natural products, or (iii) synthetic products based on MP structures. Thus, nearly half of the blockbusting pharmaceuticals are MPs or their derivatives. This statement is particularly true for the oncological and antihypertensive therapeutic areas (Cragg and Newman 2016). As reported by the World Health Organization (WHO) in May 2017, 51 antibiotics and 11 biologicals were in the clinical pipeline with 42 novel drugs, i.e., 33 antibiotics and nine biologicals. They targeted major pathogens from which seven and nine products were effective for tuberculosis (TB) and *Clostridium difficile* infections (WHO 2017).

By controlling infectious diseases and other medical conditions, secondary metabolites have had an extraordinary impact on the evolution of the pharmaceutical industry. Their use significantly increased the average life expectancy in the USA, which went from 47.3 years in 1900 to 78.93 in the year 2020 (https://www.macrotrends.net/countries/USA/united-states/life-expectancy).

Likely, the most critical usage of secondary metabolites has been as anti-infective drugs. In 2018, the market of approved antimicrobials was around 647 million dollars only in US (Fig. 1), and it is predicted to expand at a compound

annual growth rate of 3.4% (Clancy and Nguyen 2020; Carr and Stringer 2019).

Several infections affected a substantial proportion of the world population during the last years, causing thousands of deaths every year. Emerging organisms with infective capacity often confront hosts with no prior exposure and represent a novel challenge to the host's immune system. Several viruses responsible for human epidemics have been transmitted from animal hosts to humans and transferred from human to human. These infections include the human immunodeficiency virus (HIV), Ebola virus disease, hepatitis C virus, and more recently, the coronavirus. They cause many severe infectious diseases and affect human societies economic growth, development, and prosperity (Morens and Fauci 2020).

Since the secondary metabolites discovered so far come from the 1% of the cultured microbes, advances in microbial techniques have become relevant in allowing uncultured microbes to grow as potential sources of new chemical products (Newman 2016). Moreover, metagenomics (a culture-independent technique that involves the extraction and analysis of whole DNA collected from a population of microbes from different habitats) allows access to a vast untapped reservoir of genetic and metabolic diversity. This technique may include deadwood (Gómez-Brandón et al. 2017), cattle rumen and manure (Fliegerová et al. 2014; Nagler et al. 2018), aerobic and bacterial anammox granules (Xiong and Liu 2012; Dominiak et al. 2011), human epithelial cells used in forensics (Wang et al. 2017a), and plant roots (Pietramellara et al. 2013). Therefore, with this technique, the potential for discovering new molecules with chemical diversity would grow enormously.

Fig. 1 The 2018 US market for common anti-infective compounds. The graphic was elaborated based on the reports of Clancy and Nguyen 2020 and Carr and Stringer 2019
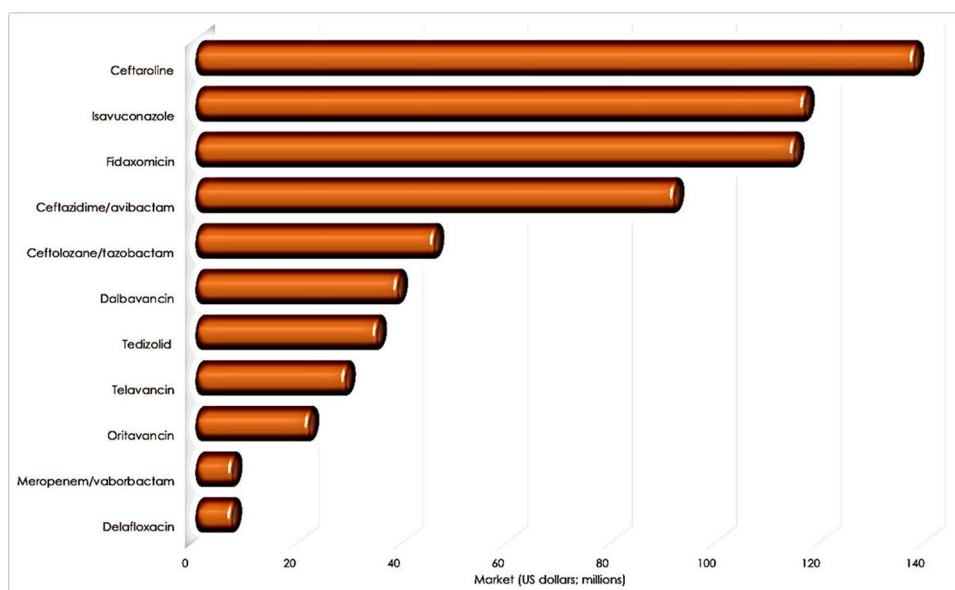
The need for new secondary metabolites

Bacterial resistance to antibiotics

The excessive amounts of antibiotics used in human therapy and those used for farm animals and aquaculture have allowed the appearance of pathogenic bacteria resistant to multiple drugs. Such resistance progressively limits the effectiveness of current antimicrobial drugs. Now, we are facing an increase in the number of reports emphasizing the development of bacterial resistance to nearly all antimicrobial agents. This situation will represent one of the leading global health concerns in the future. It is predicted to cause of approximately 10 million deaths annually in 2050, with a total cost of 100 trillion USD (Trotter et al. 2019). Although not always of high quality, the available evidence suggests a connection between personal and organizational misuse of antibiotics and the rise of resistant bacteria.

Eventually, the treatment of these emerging diseases has become increasingly complicated as microorganisms become resistant to the accessible antimicrobial options (Nordmann et al. 2011; Labro and Bryskier 2014). Over time, the specific weight supported by different antibiotic agents has ended the expansion of the auxiliary resistance mechanisms of organisms. These mechanisms include novel penicillin-restricting proteins, catalyst-dependent drug switching, transformed drug targets, and increased efflux pump expression that prompted to multidrug resistance (MDR).

In 2019, the Centers for Disease Control and Prevention (CDC) stated that in United States (US) hospitals alone, more than 2.8 million people acquire bacterial infections each year, causing 35,000 deaths https://www.cdc.gov/media/releases/2019/p1113-antibiotic-resistant.html. This number of deaths from antibiotic-resistant infections was nearly twice what was initially reported by CDC in 2013. Many cases of these infections are due to methicillin-resistant *Staphylococcus aureus* (MRSA). It caused nearly 120,000 bloodstream infections in 2017 and 20,000 associated deaths only in the USA (Kourtis et al. 2019).

MDR pathogens from the ESKAPE group (virulent MDR bacteria, including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) raise further challenges, for instance, transmissible carbapenemases such as New Delhi metallo β-lactamases in Enterobacteriaceae. Most of them are resistant to inhibition by commercially available β-lactamase inhibitors (Gootz 2010; Khan and Nordmann 2012). It is worrying that "superbugs" organisms resistant to the main antibiotics in clinical use are rapidly emerging (Khan and Khan 2016).

In recent decades, sexually transmitted diseases have also increased, especially in young people (aged 15 to 24). Examples include human papillomavirus, genital herpes, chlamydia, HIV/AIDS (Acquired Immune Deficiency Syndrome), and gonorrhea. Unfortunately, HIV/AIDS has claimed 36.3 million (27.2–47.8 million) lives worldwide. In 2020, HIV/AIDS accounts for over 1.5 million (1–2 million) diseases, with 680,000 million (480,000–1 million) deaths per year [https://www.who.int/news-room/fact-sheets/detail/hiv-aids].

Tuberculosis is a highly infectious disease caused by *Mycobacterium tuberculosis*. The rate of tuberculosis began to increase after decades of decline in the early 1990s. The currently recommended treatment for drug-susceptible *M. tuberculosis is* a 6–9-month-long regimen with a combination of four first-line drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide (Honeyborne et al. 2019). The epidemic occurred due to inadequate treatment regimens, which often lead to drug-resistant strains that represent a major threat to global public health (Abraham et al. 2020). In 2015, a 90% reduction in TB deaths and 80% in TB incidence was predicted by the WHO in its 2030 goals (WHO 2017). The goals for 2035 are reductions of 95% and 90%, respectively. A third target was that there will be no households affected by TB, and those who have TB patients have social protection to ensure that patients and their families do not incur catastrophic expenses (Floyd et al. 2018).

Therefore, new secondary metabolites are continuously required to combat antibiotic-resistant bacteria fungal and viral diseases (Andryukov et al. 2019; Chandra et al. 2017; Seukep et al. 2020).

New alternatives for Gram-positive bacteria

Renewed actions against Gram-positive pathogens have been recently taken. The lipoglycopeptides dalbavancin and oritavancin (Fig. 2) are new examples to treat Gram-positive infections. These antibiotics are used to treat infections caused by vancomycin-resistant Gram-positive microbes, including pathogens resistant to β-lactams (Sarkar and Haldar 2019). The Food and Drug Administration (FDA) approved Dalvabicin (trade name Dalvance) on May 23, 2014. In its mechanism, the antibiotic prevents the transpeptidation step during cell wall synthesis. In peptidoglycan, it binds to the C-terminal growing chain D-alanyl-D-alanine. It is effective against vancomycin-susceptible strains of *S. pyogenes*, *S. agalactiae*, and *E. faecalis*. The FDA approved Oritavancin (trade name Orbactiv) in August 2014. It is derived from chloroeremomycin, an analog of vancomycin, and due to its lipophilic side chain, it shows a prolonged half-life greater than 10 days. Oritavancin acts by disrupting the integrity of the bacterial membrane and inhibiting
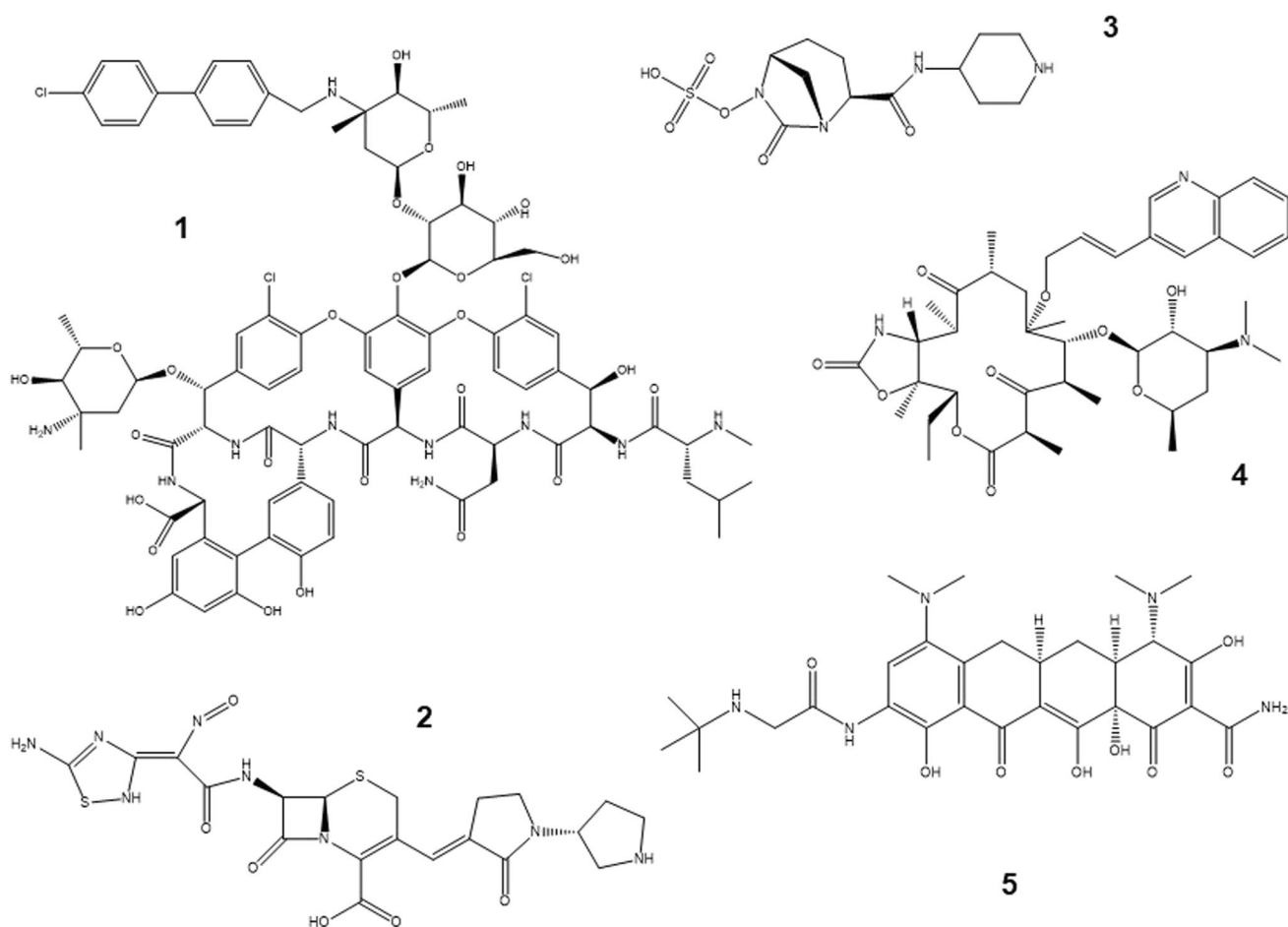
Fig. 2 Examples of structures of novel antibiotics. 1) Oritavancin, 2) ceftobiprole, 3) relebactam, 4) cethromycin, and 5) tigecycline

bacterial RNA synthesis. Its spectrum of activity mimics vancomycin but with lower MIC (minimum inhibitory concentration) values. It is effective against methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci, and vancomycin-resistant staphylococci (Koulenti et al. 2019). Dalvabicin and oritavancin can be administered in adult patients as a single intravenous dose (Saravolatz and Stein 2015).

During the last years, a range of novel modified glycopeptides was generated by semisynthetic modification of natural compounds. Among them, the eremomycin pyrrolidide shows high activity against staphylococci and enterococci, including vancomycin-resistant strains, without pseudoallergic reactions (Olsufyeva et al. 2018).

Another antimicrobial agent is ceftobiprole (trade name Zevtera/Mabeli). This antibiotic was approved by the European Medicine Agency (EMA) in October 2013 (Koulenti et al. 2019). This fifth-generation cephalosporin blocks the cell wall synthesis by binding to penicillin-binding proteins. Ceftobiprole is an effective and well-tolerated compound for treating hospital-acquired pneumonia (HAP) patients,

because of its efficacy for *S. aureus* bacteremia, acute bacterial skin infections, and community-acquired bacterial pneumonia. In 2019, ceftobiprole received the designation of Qualified Infectious Disease Product (QIDP) from the FDA.

Additional compounds for the treatment of antibiotic-resistant Gram-positive bacteria include F12. This compound is a lysin enzyme produced naturally by microbes. It represents the first next-generation compound in preclinical evaluation to treat life-threatening MRSA infections that could be used multiple times in a single patient (Zhao et al. 2020).

Another strategy involves a mixture of compounds effective against bacterial infections. Thus, a combination of imipenem, cilastatin, and relebactam (Recarbrio) has effectively treated nosocomial bacterial pneumonia. This mixture, approved on July 17, 2019, was also effective for patients with complicated tract infections who have limited or no alternative treatment options [https://www.fda.gov/news-events/press-announcements/fda-approves-antibiotic-treat-hospital-acquired-bacterial-pneumonia-and-ventilator-associated].

The glycylcyclines are further actions against resistant microorganisms, created to handle bacteria resistant to tetracyclines. These modified tetracyclines show strong activity against a broad spectrum of Gram-positive and Gram-negative bacteria, including strains carrying the two major determinants of tetracycline resistance involving efflux and ribosomal protection. The 9-*t*-butylglycylamido derivative, the *N*,*N*-dimethylglycylamido, and 6-demethyl-6-deoxy-tetracycline belong to the glycylcyclines. These antibiotics are structurally related to minocycline derivatives (TBG-MINO), exhibiting antimicrobial activity against *S. aureus* (MRSA), penicillin-resistant streptococci, and vancomycin-resistant enterococci with MIC values less than 0.5 μg/mL in which 90% of the strains show inhibition. In vivo effects of TBG-MINO against lethal infections in mice caused by isolates of *Escherichia coli*, *S. aureus*, and *Streptococcus pneumoniae* were investigated (Zhanel et al. 2004). Tigecycline (formerly GAR-936) is a semisynthetic tetracycline that shows good activity against Gram-positive cocci with 90% inhibition of penicillin-resistant strains of *S. pneumoniae* (at 0.12 μg/mL), *Enterococcus* spp. (at 0.25 μg/mL), and oxacillin-resistant *S. aureus* (at 0.25 μg/mL). Besides, respiratory pathogens such as *Moraxella catarrhalis* and *Haemophilus influenzae* are inhibited at 0.12 μg/mL and 0.5 μg/mL, respectively (Gales et al. 2005).

Telithromycin is the first orally active macrolide of the ketolides family. It shows high activity against community-acquired respiratory tract infection pathogens, irrespective of their ß-lactam, or fluoroquinolone susceptibility, initially, the FDA-approved telithromycin for the treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, and community-acquired pneumonia. However, in 2006, the FDA reduced the indications only for community-acquired pneumonia due to reports of severe drug-associated hepatotoxicity, visual disturbances, and exacerbation of myasthenia gravis (Brinker et al. 2009). The second-generation ketolide cethromycin exhibits higher antibacterial activity, even against the macrolide-resistant and telithromycin-resistant *S. pneumoniae.* There have been two major phases III clinical trials to treat mild to moderate community-acquired pneumonia. The adverse drug reactions include nausea, diarrhea, dysgeusia, and headache. However, cethromycin does not appear to cause the serious adverse effects of telithromycin (Koulenti et al. 2020).

Other common approaches are the repurposing of previously known compounds. The statin potential for host-directed therapy by modulating the immune system has been explored. Statins could be complementary when co-administered with other drugs to treat infectious diseases caused by pathogens like fungi, viruses, and bacteria. Thus, they are attractive candidates to prevent or reduce the severity of infection (sepsis, bacteremia, and pneumonia) and reduce treatment regimens. Nonetheless, it remains to be further studied those factors that could affect patient response to situations like potential interaction with other drugs and the adverse effects that this could entail (Parihar et al. 2019).

Moreover, some evidence suggests that statins may improve the treatment of infections caused by antibiotic-resistant bacteria. There are compartmentalized regions called functional membrane microdomains (FMMs) in prokaryotic cells. They are probably involved in critical cellular processes integrated by isoprenoid membrane lipids and flotillin homolog proteins. These are likely involved in the interaction with lipids and other proteins as scaffold proteins. In MRSA, FMMs are structured by the protein flotillin FloA, which supposedly participates in the association of multimeric complexes. One element of these complexes is the low-affinity penicillin-binding protein (PBPa) responsible for β-lactam antibiotic resistance. Hypercholesterolemic drugs like statins may compromise the FMM integrity by hindering these membrane domain lipid biosynthesis. This property, in turn, affects PBP2a oligomerization, resulting in MRSA infections sensitive to penicillin antibiotic treatments. Repurposing statins could be an approach to improve conventional antibiotic therapies. However, lipid biosynthesis of these membrane microdomains is not universal in bacteria, so statins do not appear to be inherently bactericidal (García-Fernández et al. 2017).

Regarding tuberculosis therapy, a rapid selection of *M. tuberculosis* mutants carrying changes in specific genes that confer resistance to first-line antimicrobials has been observed. For example, resistance to pyrazinamide in this pathogen is due to mutations in the gene encoding pyrazinamidase (Tahir et al. 2020). Latest developments in tuberculosis antimicrobial agents include avermectins and fluvastatin Mourenza et al. (2020). Avermectins are highly active anthelmintic macrolides against MDR strains of clinical isolates of *M. tuberculosis.* They reduce the initial bacterial viability up to 6 orders of magnitude, showing MIC_{90} values against different resistant isolates ranging from 6 to 8 μg/mL (Lim et al. 2013). Avermectines are approved for clinical and veterinary uses.

Fluvastatin is a lipid-lowering statin with antilipidemic and antimicrobial properties (Perihar et al. 2019). It inhibits the conversion of hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate, a key step in cholesterol synthesis. Cholesterol is essential for the internalization of mycobacteria into host cells (Gatfield and Pieters 2000). Statins modulate immune responses by suppressing major histocompatibility complex II slightly inducing the release of TH1 cytokines, promoting the activation of caspase 1, and strengthening the host response against *M. tuberculosis.*

Recently, an industry and academic collaboration, using previously uncultured soil microbes, identified three novel

compounds (streptomycobactin, kitamycobactin, and amycobactin) effective against *M. tuberculosis* (Quigley et al. 2020). Kitamycobactin (an analog of lassomycin) targets the mycobacterial ClpP1P2C1 protease. This group further defines the mechanism of action of amycobactin, demonstrating that it inhibits protein secretion via the Sec translocation machinery.

Novel alternatives for Gram-negative bacteria

Infections caused by drug-resistant Gram-negative bacilli are a critical public health threat. Unfortunately, the available drugs to treat these infections (colistin, fosfomycin, aminoglycosides, and tigecycline) have a limited efficacy and safety profile and induce bacterial resistance. Thus, developing new active drugs against these pathogens has become a priority. A decade ago, the Infectious Diseases Society of America issued the 10 X'20 Initiative to develop ten new antibiotics by 2020 [https://doi.org/10.1086/652237].

For several years, a successful strategy in treating bacterial infections has been "combination therapy." This approach involves the use of an antibiotic plus an inhibitor capable of blocking the primary mechanism of bacterial resistance. This strategy has been helpful to increase the efficacy of some β-lactam antibiotics since β-lactamase enzymes are responsible for a large proportion of the bacterial resistance phenotype. *Streptomyces clavuligerus* produces clavulanic acid with a bicyclic ß-lactam ring attached to an oxazolidine ring with oxygen instead of a ß-hydroxyethylidene sulfur substituent at C-2 and lacks an acylamino group at C-6. First described in 1976, this antibiotic exhibited potent inhibition of the β-lactamases synthesized by staphylococci and β-lactamases mediated by plasmids from *E. coli*, *Klebsiella*, *Shigella*, *Pseudomonas*, *Proteus*, and *Hemophilus* (Breijyeh et al. 2020). Clavulanic acid is a β-lactamic compound with low antibacterial activity. However, as a ß-lactamase inhibitor, this molecule has been combined with broad-spectrum semisynthetic penicillin drugs. For instance, when administered with amoxicillin, it is marketed under the brand name Augmentin to treat infections caused by pathogenic β-lactamase-producing bacteria (Worthington and Melander 2013). However, its spectrum is limited to class A β-lactamases and does not include carbapenemases from *K. pneumoniae* (Papp-Wallace 2010). Fortunately, there are now new classes of inhibitors in the clinic, and more compounds and combinations are being developed. Boron-based compounds, especially the cyclic boronate taniborbactam, are the current alternatives against the most aggressive pathogens. When these compounds are combined with cefepime, they show a broad-spectrum of activity against a wide range of serine-β-lactamases and relevant metallo-β-lactamases (González-Bello et al. 2020). Besides, a breakthrough is the sulbactam/durlobactam combination

for infections caused by *A. baumannii*. Another example is the new orally available diazabicyclooctane (ETX0282), which inhibits class A, C, and D serine β-lactamases. Combined with cefpodoxime or CDP4, it is an effective therapy for treating MDR and carbapenem-resistant bacterial infections (Durand-Réville et al. 2020).

Nosocomial bacteria are microbes that inhabit hospitals, including Gram-positive and Gram-negative pathogens. More than 60% of hospital sepsis are caused by Gram-negative bacteria (*Klebsiella*, *Escherichia*, *Enterobacter*, *Serratia*, *Citrobacter*, *Salmonella*, and *Pseudomonas*) and have become a major threat to public health (Dolin et al. 2019; Rannikko et al. 2017). Among them, *Pseudomonas aeruginosa* accounts for approximately 80% of these opportunistic infections. They are a severe problem in hospitalized patients with cancer, cystic fibrosis, and burns, causing death in 50 percent. *Pseudomonas* species are naturally MDR bacteria that can cause infections like pneumonia and endocarditis. They also cause infections of the urinary tract, central nervous system, wounds, eyes, ears, skin, and musculoskeletal system. Although many bacteria are sensitive to gentamicin, tobramycin, and amikacin, resistant strains constantly develop. Thus, the frequency of MDR pathogenic bacteria increases, making hospitals "dangerous places to be, especially if you are sick, but even if not" (Van Duin and Paterson 2016). Concrete actions against this resistance are the development and approval of several antibiotics. These included Ceftaroline fosamil on October 29, 2010; Tedizolid phosphate on June 20, 2014; Oritancancin on August 6, 2014; Ceftozolane and Tazobactam on December 19, 2014; Ceftazidime and Avibactam on February 25, 2015. Besides, Dalofloxacin on June 17, 2017; Meropenem and Vaborbactamin on August 30, 2017; Plazomicin on June 26, 2018; Eravacycline on August 27, 2018; Omadacycline, approved on October 2 and active against Gram-positive and Gram-negatives, 2018 and Lefamulin, approved on August 19, 2019. Cefiderocol is a siderophore cephalosporin active against carbapenem-resistant Gram-negatives. It is a modified cephalosporin (approved on November 14, 2019) with one pyrrolidinium group and one carboxypropanoxyimino located at the 3 and 7 positions of the cephem nucleus (Zhanel et al. 2004). This compound enters the bacterial periplasm by attaching to penicillin-binding proteins due to its siderophore-like property, causing inhibition of cell-wall synthesis. [https://www.contagionlive.com/view/have-we-made-progress-in-the-10-20-initiative].

Although there is a steady increase in resistance to most current antibiotics in almost every pathogen over time, not all antibacterial agents exhibit the same rate of resistance development. For example, antimicrobials such as rifampicin, which targets single enzymes, are the most susceptible to the development of resistance. In contrast,

resistance to agents such as penicillin, which irreversibly inactivate multiple targets, develops slowly.

Fungal infections

More than 150 million infections by fungi occur worldwide every year (Kainz et al. 2020). Pathogenic yeasts are also a problem. The main etiologic agent associated with nosocomial candidiasis is *Candida albicans*. The estimated global burden of candidaemia is 159,253 cases across 39 countries (Bongomin et al. 2017).

Fungi are harmless most of the time, but they can occasionally provoke infections named mycoses, where the fungi surpass human or animal resistance barriers. Generally, these infections are not life-threatening. However, when they are invasive and spread, they cause more severe infections, such as in critically ill patients and people treated with drugs that disrupt the immune system. Besides, the use of antineoplastic and broad-spectrum antibiotics, prosthetics and grafts, and more aggressive surgeries has augmented invasive fungal infections. Patients with burns, pancreatitis, neutropenia, or post-organ transplantation (62–91% liver, 28–55% heart, 6–38% pancreas, and 20% kidney) are also predisposed to fungal infections (Silveria and Husain 2007). About 40% of the nosocomial deaths are due to fungal infections, and *Aspergillus* and *Candida* cause 80%. Also, *Cryptococcus* spp., *Fusarium* spp., *Scedosporium* spp., *Penicillium* spp., and zygomycetes are increasingly involved (Badiee and Hashemizadeh 2014; Bougnoux et al. 2018; Khan et al. 2017). Pneumonia caused by *Pneumocystis carinii* remains the leading common AIDS-associated infection worldwide (Pereira-Díaz et al. 2019; Huang et al. 2011). Patients undergoing a bone marrow transplant can have severe complications because of pulmonary aspergillosis.

The emergence of increased resistance to fungi and the increasing incidence of invasive fungal infections have led to the search for novel antifungal compounds (Sanchez and Demain 2017a). Although amphotericin B is the first-line treatment for systemic infections (because of its broad-spectrum and fungicidal activity), significant side effects limit its clinical utility. Additional compounds with antifungal activity are the echinocandins. These are large lipopeptide molecules that inhibit the synthesis of 1,3-β-D-glucan by disrupting the fungal cell wall (Yoshimi et al. 2017). Three echinocandins have reached the market, i.e., caspofungin (pneumocandin or MK-0991), anidulafungin, and micafungin. Caspofungin exhibits higher activity and lower toxicity than amphotericin B. Its activity included isolates resistant to azoles and amphotericin B. Some filamentous fungal species like A*spergillus*, a few dimorphic fungi (*Histoplasma*, *Blastomyces*), *Candida*, *P. carinii*, and *Coccidioides* were also affected (Letscher-Bru and Herbrecht 2003).

Regarding anidulafungin, it is currently licensed in the USA and has proven efficacy against esophageal candidiasis and invasive infections by *Candida* and *Aspergillus* (Ikeda et al. 2007). As for micafungin, it has been licensed for clinical use in Asian countries and the USA. This drug exhibits extremely potent antifungal activity against clinically relevant fungi, including *Aspergillus* and azole-resistant strains of *Candida* (Wang et al. 2017b). In animal studies, micafungin is as effective as amphotericin B in recovering survival rate. A linear pharmacokinetic profile distinguishes it with less toxic effects.

Although several new antifungal drugs have been introduced in the last six years, some patients remain resistant to treatments. This resistance is primarily due to intrinsic or acquired antifungal resistance, organ dysfunction that precludes the use of some agents, and drug interactions. Besides, some drugs penetrate poorly into sanctuary sires like the eye and central nervous system (Pasqualotto and Denning 2008). Nonetheless, there are some improvements in the development of new compounds. Among these advances, we can mention posaconazole, a new member of the class of triazole antifungals with a favorable toxicity profile. Posaconazole is a broad-spectrum antifungal agent that inhibits ergosterol biosynthesis. It has demonstrated clinical efficacy in the treatment of oropharyngeal candidiasis. It has the potential to be used as salvage therapy for various aggressive fungal infections like invasive aspergillosis, zygomycosis, and cryptococcal meningitis. A combination of posaconazole with caspofungin or the calcineurin inhibitor FK506 exhibits synergistic effects against the human fungal pathogen *C. albicans* (Chen et al. 2013).

Despite the importance of infectious diseases, big pharmaceutical companies have lost interest in developing new antibiotics. However, anti-infectives are still big business, and therefore, there is a need to develop new antimicrobials. Between 2010 and 2019, some small pharmaceutical and biotechnology companies introduced novel antibacterial compounds, which have evolved into attractive sales (Table 1).

In addition, to tackle antibiotic resistance, new families of antibiotics must enter the market at regular intervals to address new diseases produced by evolving pathogens. At least 30 new diseases have appeared between 1980 and 1990, and their incidence is increasing.

Antiviral infections

Among many of the danger infectious that people faces today, viruses represent a serious problem that threatens deadly global pandemics. Viral diseases are emerging and spreading widely due to changes in global environments and the evolution of transport systems. Although understanding

Table 1 Applications and sales of some antimicrobials approved between 2010 and 2019

Brand name	Agent	FDA approval	USD millions	Class	Treatment
Teflaro	Ceftaroline	October 2010	138.00	5th-generation cephalosporin	ABSSSIs, CABP
Cresemba	Isavuconazole	March 2015	117.00	Azole class antifungal	Invasive aspergillosis and invasive mucormycosis
Dificid	Fidaxomicin	May 2011	115.00	Macrolide	*Clostridioides difficile*-associated diarrhea
Avycaz	Ceftazidime/avibactam	February 2015	92.00	β-lactam/β-lactamase inhibitor	cIAI, cUTI including pyelonephritis, HABP, VABP
Zerbaxa	Ceftolozane/tazobactam	December 2014	46.00	β-lactam/β-lactamase inhibitor	HABP, VABP
Dalvance	Dalbavancin	May 2014	39.00	Lipoglycopeptide	ABSSSIs
Sivextro	Tedizolid	June 2014	35.00	Oxazolidinone	ABSSSIs
Vibativ	Telavancin	September 2009	29.00	Lipoglycopeptide	HABP, VABP, cSSSI
Orbactiv	Oritavancin	August 2014	22.00	Lipoglycopeptide	ABSSSIs
Vabomere	Meropenem/vaborbactam	August 2017	7.30	Carbapenem β-lactamase inhibitor	cUTI including pyelonephritis
Baxdela	Delafloxacin	June 2017	7.20	Fluoroquinolone	ABSSSIs
Xerava	Eravacycline	August 2018	5.9	Fluorocycine	cIAI
Zemdri	Plazomicin	June 2018	NA	Aminoglycoside	cUTI including pyelonephritis
Recarbrio	Imipenem-cilastatin-relebactam	July 2019	NA	New antibacterial combination	cUTI including pyelonephritis
Fetroja	Cefiderocol	November 2019	NA	Siderophore cephalosporin	cIAI, cUTI including pyelonephritis, HABP, VABP

of viral biology and physiology has increased in recent years, several infections affected a substantial proportion of the world's population, causing thousands of deaths every year.

Some viruses are frequently involved in respiratory infections. Typical examples are the respiratory syncytial virus, human parainfluenza viruses 1 and 3, influenza viruses A and B, and some adenoviruses. Some viral diseases severely damage economic, social, and human conditions, including those caused by HIV, Ebola virus, hepatitis C virus, and coronavirus. They produce millions of deaths and many serious illnesses, affecting the economic growth of human society, their development, and prosperity. The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Apparently, it has a zoonotic origin; the hosts' animals are rodents and bats, while other animals such as civets, raccoon dogs, camels, and possibly pangolins play a role in transmission as intermediate hosts (Amoutzias et al. 2022; Guo et al. 2020; Lau and Chan 2015). Therefore, there is a constant requirement for new antiviral compounds.

The global antiviral drug treatment market report is estimated to reach a cost of nearly USD 75.33 billion by 2027 from about USD 52.21 billion in 2019, growing at a compound annual growth rate of approximately 4.69% between 2020 and 2027 [https://www.pharmiweb.com/press-release/2020-08-19/antiviral-drugs-treatment-market-to-develop-stunningly-and-reach-about-usd-7533-billion-by-2027-z].

Natural substances continue to be primary sources for prototype antimicrobial and antiviral drugs, although many chemically synthesized drug basic structures owe their origin to natural sources. Among antimicrobial drugs, antivirals represent more than 20% of the market. Two antivirals initially acquired from sea sponges are currently obtained by chemical synthesis. One is acyclovir, which is effective against the herpes virus and HIV. It inhibits and inactivates the DNA polymerase of the virus (Vanpouille et al. 2012). The other is cytarabine, effective against acute myeloid leukemia (Momparler 2013). Both metabolites are nucleoside analog drugs (Jiménez et al. 2018).

With up to 37 million people living with HIV worldwide, HIV infection poses a serious public health risk. Even though a combination of antiretroviral therapy provides stable viral suppression, it is not devoid of undesirable side effects, especially in persons undergoing long-term treatment. Screening natural products derived from various species have afforded metabolites with notable antiviral activity against HIV. Among them, γ-pyrone Aureothin is a natural polyketide produced by *Streptomyces thioluteus*. It harbors a γ-pyrone group and a tetrahydrofuran ring separated from a 4-nitro phenyl group by a diene backbone. Aureothin was identified as a successful candidate through a single-dose (10 μM) screening and validated by evaluating the dose dependence of HIV inhibitory activities. Aureothin ($IC_{50} = 5.3 \pm 0.40$ nm) showed robust anti-HIV activity, comparable or only moderately lower than that of several clinical

drugs assayed in parallel (the protease inhibitor Saquinavir, $IC_{50} \sim 10$ nm), the reverse transcriptase inhibitor Efavirenz and the integrase inhibitor Dolutegravir (each ~ 1 nm). A drawback of this compound is its high sensitivity to light. However, several Aureothin molecules with fluorinated or chlorinated derivatives have been synthesized with better photostability than the original compound, retaining more than 95% of anti-HIV activity after illumination. In one of these derivatives, trifluoromethyl replaces the nitro group and inhibited the accumulation of uncleaved and partially spliced mRNAs, preventing the production of all major components of virus particles. The mode of action of this compound is different from all current clinical anti-HIV drugs. It shuts down de novo virus production by inhibiting HIV gene expression and effectively inhibits a spectrum of clinical isolates, including all HIV genotypes (HIV-type 1 and HIV-type 2) (Herrmann et al. 2020).

In its pathogenesis, HIV-1, like other retroviruses, depends on its stable integration into the host genome to efficiently replicate the viral RNA and, hence, keep the infected state. Therefore, the new viral DNA synthesized during reverse transcription is quickly integrated into the host cell genome (through a step called "integration"), allowing transcription of viral RNA. In the late HIV viral replication phase, a viral protease cleaves the large polyprotein precursor GagPol. This action enables the maturation of the viral particle and infectivity. Non-infectious viral particles result when the precursor Gag polyprotein is not cleaved adequately. Therefore, the US National Cancer Institute (NCI) has directed an enormous effort to explore natural metabolites that inhibit HIV reverse transcriptase and protease. These products are the primary agents currently used to contain HIV. Besides, the NCI has evaluated the HIV-1 inhibitory activity of pepstatin A, a small pentapeptide synthesized by several species of *Streptomyces*. This compound that contains a rare amino acid (4-amino-3-hydroxy-6-methylheptanoic acid) sterically blocks the active site of HIV-1 protease (Yang et al. 2001; Matúz et al. 2012). Recently, a linear peptide (ahmpatinin ^{i}Bu) isolated from *Streptomyces* sp. has been reported as an effective HIV-1 protease inhibitor with an IC_{50} value of 1.79 nM (Chen et al. 2018).

In the late 2019, an ongoing outbreak of pneumonia cases was reported in Wuhan, China. This infection was caused by a novel coronavirus associated with the severe acute respiratory syndrome coronaviruses. Therefore, it was designated SARS-CoV-2 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020). This viral disease became a pandemic in February 2020. Researchers worldwide have responded by studying physiology of the virus in different settings and testing all kinds of approved antiviral drugs to tackle the disease or develop novel compounds to inhibit viral spread (Ciliberto and Cardone 2020). All sorts of scientific specialists were involved in this task,

including immunologists, epidemiologists, microbial biotechnologists, pharmacologists, mathematicians, physicists, and engineers. They decided to change their main research interest to offering solutions for the COVID-19 pandemic. In support of this action, government and international funds became available to capitalize on global efforts to develop many potential solutions. In parallel, people from the industry entered alone or associated with Universities or Biotechcompanies to emerge with diagnostic tests and the production of specific vaccines [https://publications.iadb.org/publications/english/document/Responding-to-COVID-19-with-Science-Innovation-and-Productive-Development.pdf], as possible solutions to rapidly stop or alleviate the enormous number of deaths caused by COVID-19. Unfortunately, fast-spreading variants are emerging (Burki 2021), and scientists should attempt new treatment alternatives.

Experts in microbial biotechnology have the tools to lead the second wave of efforts against SARS-CoV-2 and related variants. Recent progress in synthetic and systems biology has supported the field by introducing new and unprecedented tools that, when combined with iterative pipelines, may increase chemical alternatives and industrial production of bioactive compounds, such as antivirals (Martinez 2020).

Using these tools, structurally different compounds like terpenes, polysaccharides, polyketides, and peptides that inhibit RNA and DNA viruses have been isolated from various microorganisms like fungi and actinobacteria using these tools (Zaporozhets and Besednova 2020). These compounds can prevent the coronavirus entry into the cell or the release of virions out of the cell. They can even inhibit the viral proteins or disrupt the viral genome replication. The diversity of these chemical classes is related to their different mechanisms to inhibit coronaviruses (Zaporozhets and Besednova 2020).

The spherical capsid envelops a positive-strand RNA genome of about 30 kb which is considered the largest of its kind. It contains two replicase proteins cleaved by a major viral protease (M^{pro}), a highly conserved molecular target in coronaviruses (Hoffmann et al. 2020). Earlier reports on viral protease inhibitors like the HIV protease inhibitor lopinavir revealed significant anti-SARS-CoV-2 activities in vitro (Choy et al. 2020).

An extensive database of specialized microbial natural products (The Natural Product Atlas) containing more than 24,000 different compounds has been used to detect natural ligands that could block the active site of M^{pro} (Sayed et al. 2020).

Analysis of ligands with the highest M^{pro} score indicated that several compounds were potentially effective against SARS-CoV-2 (Lipinski 2004). Among them, the polyketide citriquinochroman, produced by the endophyte *Penicillium citrinum*, and the indolocarbazole alkaloid holyrine B, produced by a marine actinomycete (Fiedler et al. 2008), can be

distinguished. The third best compound is the aminofuran proximicin C, isolated from the actinobacteria *Verrucosispora* MG-37 (Fiedler et al. 2008).

The contribution of other known compounds to the treatment of COVID-19 has been explored. Recently, an additional use for statins has been reported by Daniels et al. (2020). This group found that using statin before hospital admission in COVID-19-infected people was associated with a more than 50% reduction in risk of developing severe disease symptoms. Thus, patients with COVID-19 who took statins fared better. Statins decrease COVID-19 severity, likely by removing cholesterol that the virus uses to infect. The researcher's findings support that the statin use before hospital admission for COVID-19 reduced by more than 50 percent the risk of developing severe COVID-19 (Daniels et al. 2020).

Therefore, although vaccines have been developed, antivirals are still needed to combat the infection of this virus.

Additional needs of secondary metabolites

Over the years, the pharmaceutical industry has extended its antibiotic screening programs to look for other antibiotic applications in medicine and agriculture (Davies and Davies 2010; Berdy 2012; Pham et al. 2019; Demain and Martens 2017). As a result of this movement, some of the main essential products of the pharmaceutical industry have been obtained. For example, immunosuppressants have revolutionized medicine by enabling organ transplantation (Watson and Dark 2012; Duncan and Wilkes 2005). Other applications comprise hypocholesterolemic agents, antitumor drugs, and other pharmacological activities (Fig. 3). Catalyzed by simple enzymatic assays for pretest detection in intact animals or in the field, further applications are increasing in several areas of pharmacology and agriculture. In 2013, more than 15 secondary compounds were derived from

marine fungi in clinical trials (Bhatnagar and Kim 2013). Interestingly, many of the 300 new natural products isolated from marine sources were polyketides.

Hypocholesterolemic drugs of microbial origin

Atherosclerosis is a chronic, progressive disease typified by a continuous accumulation of atheromatous plaques within the arterial wall, causing stenosis and ischemia. The last two decades have testified to the introduction of a variety of antiatherosclerotic therapies.

Statins are hypolipidemic drugs that lower blood cholesterol levels. They inhibit the HMG-CoA reductase, a mevalonate pathway enzyme involved in cholesterol synthesis. Inhibition of HMG-CoA reductase in the liver stimulates low-density lipoprotein (LDL) receptors, causing an increased LDL clearance from the bloodstream and decreased blood cholesterol levels. Their cholesterol-lowering effect reduces the risk of cardiovascular disease, prevents stroke, and drops peripheral vascular disease (Pollak and Kramer 2012). Besides, statins have an anti-thrombotic and anti-inflammatory effect.

Currently, there are several statins in clinical use with an annual market of almost $30 billion. The first member of the statins group (compactin or mevastatin) was isolated as an antibiotic product from *Penicillium brevicompactum* and later from *Penicillium citrinum*. Although compactin was not commercially significant, its derivatives achieved substantial medical and commercial success (Endo 2010).

The lactone form of mevalonic acid (known either as lovastatin, monacolin K, mevinolin, or Mevacor™) can be extracted from broths of *Monascus rubra* and *Aspergillus terreus* (Manzoni and Rollini 2002). Lovastatin, developed by Merck & Co., and officially approved by the FDA in 1987, was the first commercially marketed statin. Lovastatin has a hexahydronaphthalene chemical skeleton in its chemical structure, substituted with a p-hydroxy-lactone moiety. A

Fig. 3 Applications of natural products
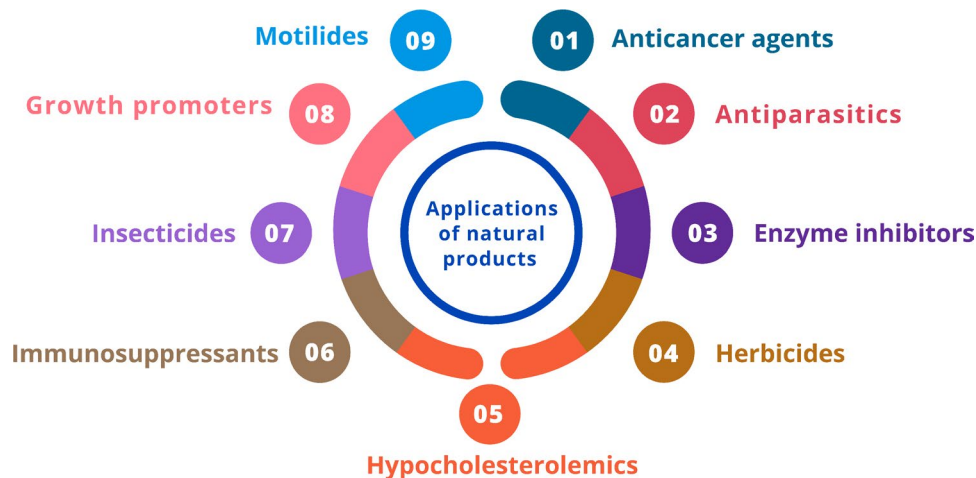
semisynthetic derivative of lovastatin with significant hypocholesterolemic activity is Zocor™ (simvastatin). Before becoming generic, the industry reported drug sales for 7 billion dollars per year. Simvastatin production usually starts from lovastatin in a multistep chemical process. However, an enzymatic bioconversion procedure using recombinant *E. coli* has been developed (Xie and Tang 2007). Pravastatin (3.6 billion dollars per year) can be produced via different biotransformation processes from compactin by *Streptomyces* sp. (Park et al. 2003), *S. avermitilis* (Yao et al. 2017), and *Penicillium chrysogenum* (McLean et al. 2015). Other genera involved in the manufacture of statins are *Doratomyces*, *Eupenicillium*, *Gymnoascus*, *Hypomyces*, *Paecilomyces*, *Phoma*, *Trichoderma*, and *Pleurotus* (Alarcon et al. 2003). A synthetic compound modeled from the natural statins' chemical structure is Lipitor, the leading drug of the whole pharmaceutical industry in terms of the market (about 14 billion dollars per year) for many years.

Microbial drugs used in clinical practice as anticancer therapy

In 2020, over 19.3 million new cancer events were diagnosed in the world. A 19% higher incidence corresponded to men than women, and deaths for this number ascended to 43%, with variations depending on the world region. The tumor classes with the highest frequency were breast (11.7%), lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) (Sung et al. 2021). Over 60% of the anticancer drugs in clinical use are natural products derived from microorganisms. The drugs started to appear around 1940 with the discovery of actinomycin from *Streptomyces antibioticus*. Since then, many anticancer compounds have been isolated from natural sources and introduced into clinical practice. Relevant antiproliferative examples are daunorubicin, doxorubicin, epirubicin, pirarubicin, valrubicin (anthracyclines), bleomycin (RSP), mitomycin C (azidine-containing compounds), piclamycin (anthracenones), streptozotocin (nitroso-urea compounds), pentostatin (purine analog), calicheamicin (endiynes), camptothecin (indole alkaloid), Taxol and epothilones (taxanes), and romidepsin (depsipeptide). Among these drugs, some novel anticancer drugs of microbial origin and clinical relevance deserve particular attention. These include anthracyclines, licheamicin, camptothecin, the taxanes (Taxol and epothilones), and the depsipeptide romidepsin.

Some of the most efficient antitumor agents ever developed are anthracyclines. They are effective against more types of cancer (leukemias, lymphomas, breast, ovarian, uterine, and lung cancers) than any other chemotherapy agents (Kadurin et al. 2017). Regarding their mechanism of action, anthracyclines inhibit the synthesis of DNA and RNA in the target cells. They form a complex by intercalating in DNA strands. They trigger DNA cleavage by topoisomerase II, resulting in mechanisms that conduct to cell death. In their cytotoxicity, the binding to cell membranes and plasma proteins performs a critical role. The first anthracycline discovered was daunorubicin (daunomycin), naturally produced by *Streptomyces peucetius*. Doxorubicin (adriamycin) is a 14-hydroxylated version of daunorubicin, approved by the FDA in 1974. It shows a better activity against solid tumors and a higher therapeutic index. Their major adverse effects are heart damage (by dose-dependent cardiotoxicity, which is cumulative and irreversible), and vomiting, which considerably restricts their usefulness (Henriksen 2018). Anthracycline treatment also induces drug resistance even at the desired cumulative dose. Many semisynthetic analogs resulting from the aglycone and sugar moiety chemical modifications were developed to deal with the undesirable effects. However, despite the numerous efforts, only some of them reached the stage of clinical development, and even fewer achieved marketing approval. Epirubicin (Ellence®) is privileged over doxorubicin as it causes fewer side effects and shows better elimination. The epirubicin structure has a different spatial orientation of the hydroxyl group at the 4′ carbon of the sugar, explaining its faster elimination and reduced toxicity. Epirubicin is beneficial against breast and ovarian cancer, lung cancer, gastric cancer, and lymphomas. However, this compound may cause severe heart problems during cancer treatment or after treatment ends. An additional analog is Valrubicin (Valstar), which is the N-trifluoroacetyl, 1–4-valerate derivative of doxorubicin. Although Valstar was removed from the market in 2002 due to manufacturing problems, it was placed back on the FDA Drug Shortage List in 2007, after it was considered a medical need.

An analog of daunorubicin is idarubicin. It lacks the C-4 methoxy group of the natural compound, and this increases its lipophilicity. Idarubicin has improved activity as induction therapy for acute myelogenous leukemia and some solid tumors. This improvement probably results from its increased lipophilicity and cellular uptake. Due to its formulation with thermosensitive liposomes, the drug is rapidly released in mild hyperthermia, improving the tumor regression (Lu et al. 2021). Similarly, an effective tumor relapse by doxorubicin can be observed using single low-dose treatment with hyperthermia-activated liposomal doxorubicin (Tagami et al. 2011). This treatment increases drug uptake by 5.2-fold compared to free doxorubicin and reduces its heart delivery by 15-fold.

Several new anthracyclines are currently in clinical trials against prostate cancer and leukemia (Bigagli et al. 2018; Tantawy et al. 2020).

Calicheamicins are additional anticancer drugs of the enediyne family produced by *Micromonospora echinospora*. Their antitumor mechanism is probably due to the

double-stranded DNA cleavage (Elshahawi et al. 2014). They are extremely toxic, but it was possible to introduce one such compound into the clinic by ingeniously attaching it to a monoclonal antibody for selective delivery to cancer cells. The monoclonal antibody binds to a transmembrane receptor (CD33) expressed in monocytic/myeloid lineage cells. Most leukemic blast cells express CD33, but the amount diminishes with maturation in normal hematopoietic cells. In this regard, gentuzumab ozogamicin (marketed as Mylotarg™) was developed to treat acute myelogenous leukemia (AML). In 2000, the FDA approved this drug for patients over 60 years old with relapsed AML who are not considered candidates for standard chemotherapy. However, the monoclonal antibody drug linker was unstable, and 50% of the bond drug was released in 48 h. Thus, the FDA removed this drug from the market due to safety concerns (Panowski et al. 2014). Later in September 2017, the FDA approved the low dose of gemtuzumab ozogamicin in chemotherapy for the treatment of CD33 positive refractory AML (Nagayama et al. 2017).

Camptothecin is a modified monoterpene indole alkaloid that has been used in traditional Chinese medicine. Isolated from the *Camptotheca acuminate* tree, this drug was chosen by its antitumoral activity against an animal leukemia model (Asano et al. 2009). However, considering the quantities required for the pharmaceutical industry worldwide, the yield of camptothecin extracted from plants was insufficient (Martino et al. 2017). An endophytic fungus isolated from the plant *Nathapodytes foetida* (*Entrophospora infrequens*) also produces camptothecin. Because of the low concentration of camptothecin in tree roots and poor yield from chemical synthesis, fungal fermentation is very promising for its industrial production. The drug is used for recurrent colon cancer and has unusual activity against lung, ovarian, and uterine cancer (Li et al. 2017a). The cellular target of camptothecins is the type I DNA topoisomerase since it shows increased levels in cancer cells compared with normal cells. The enzyme inhibition mechanism occurs by noncovalent binding of camptothecins to the complex topoisomerase-DNA, producing irreversible DNA strand breaks and causing cell death (Martino et al. 2017).

Camptothecin is known commercially as Camptosar™ and Campto™ and accomplished sales of $1 billion in 2003 (Lorence and Nessler 2004). Irinotecan and topotecan are two water-soluble camptothecin derivatives approved by the FDA in 2015. Metastatic colorectal neoplasia responds to irinotecan. Topotecan is used for ovarian cancer, cervical cancer, and small-cell lung cancer. When the patients become resistant to irinotecan, the combination with the monoclonal antibody Erbitux (Cetuximab) can extend the use of this compound. This antibody blocks a protein that stimulates tumor growth, and therefore, its combination with irinotecan helps patients with metastatic colorectal cancer

express the epidermal growth factor receptor. This protein factor is expressed in 80% of advanced metastatic colorectal cancers. The drug combination decreases the invasion of normal tissues by tumor cells and the spreads of tumors to new areas. Today, one of the most successful nonactinobacterial cancer-fighting molecules is paclitaxel (sold as Paxene®, Taxol®), which was first isolated from the Pacific yew tree, Taxus brevifolia. Taxol® is a steroidal alkaloid diterpenoid. It has a N-benzoylphenyl isoserine side chain and a tetracycline ring. This compound inhibits fast-dividing mammalian cancer cells by stimulating tubulin polymerization and interfering with normal microtubule breakdown during cell division. The benzoyl group of the molecule is particularly essential for maintaining its potent bioactivity.

Taxol® also inhibits several fungi (*Pythium*, *Phytophthora*, and *Aphanomyces*) by a similar mechanism. Taxol was approved in 1992 for refractory ovarian cancer, and today is used against breast cancer and advanced forms of Kaposi's sarcoma (Benbrahim et al. 2013). Paclitaxel has seized $3.7 billion annual sales in international markets. Moreover, a new formulation in which paclitaxel is bound to albumin is sold under the trademark Abraxane. The net sales worldwide of this product increased by 9% between 2016 (973 million dollars) and 2018 ($1,062 million dollars) [https://ir.celgene.com/press-releases-archive/press-release-details/2019/Celgene-Reports-Fourth-Quarter-and-Full-Year-2018-Operating-and-Financial-Results/default.aspx].

A low production level of Taxol is obtained from the yew tree, ranging from 0 to 0.069% of the dry weight. In order to meet the commercial requirements of Taxol, some *Taxus* species have been endangered, which pressed to find other sources of this natural product (Li et al. 2017b). Although synthetic procedures for Taxol production have been tried, the chemical molecular structure is so complex that commercial synthetic production is unachievable. Taxol production by cell culture of *Taxus* sp. amounted to 67 mg L^{-1} (Sabater-Jara et al. 2010). Currently, Italy, the UK, the Netherlands, and other Western countries are involved in Taxol production by plant cell fermentation technology.

Although initially discovered in plants, Taxol has also been discovered to be a fungal metabolite. Fungi from genera such as *Alternaria*, *Aspergillus*, *Cladosporium*, *Fusarium*, *Nodulisporum*, *Penicillium*, *Pestalotiopsis*, *Phoma*, *Phomopsis*, *Phyllosticta*, *Taxomyces*, *Trichoderma*, and *Tubercularia* produce Taxol (Naik 2019). However, Taxol-producing fungi may lose the ability to synthesize this compound. Soliman and Raizada (2018) have shown in the endophyte fungi *Paraconiothyrium* that this compound production is inhibited by light, resembling the conditions in which the fungus is found in nature.

Some elicitors can enhance Taxol production. Thus, supplementation of the endophyte *Pestalotiopsis microspora* (isolated from the tree *Taxodium mucronatum*) culture

medium with 300 µM salicylic acid increases 45-fold its production. This increase (625.5 µg L^{-1}) correlates well with the transcription levels of the geranylgeranyl pyrophosphate synthase gene, which is involved in Taxol biosynthesis (Subban et al. 2019). In another study (Qiao et al. 2017), supplementing the culture media with NaOAc, Cu^{2+}, and salicylic acid increased the Taxol yield in the endophytic fungus *Aspergillus aculeatinus* Tax-6 (isolated from *Taxus chinensis* var. *mairei*) from 334.92 to 1337.56 mg L^{-1}.

On the other hand, production by submerged fermentation was reported at 417 µg L^{-1} levels with an engineered strain of the fungus *Ozonium* sp. (EFY-21). The transformed fungus overproduced the Taxol rate-limiting enzyme taxadiene synthase (Wei et al. 2012). Another endophytic strain, *Phoma betae*, isolated from the medicinal tree *Ginkgo bilova*, produced Taxol at 795 µg L^{-1} (Kumaran et al. 2012). *Cladosporium cladosporoides*, an endophyte fungus of the *Taxus media* tree, produces 800 µg L^{-1} of Taxol (Zhang et al. 2009). Furthermore, *Metarhizium anisopiliae* H-27, isolated from the tree *Taxus chinensis* yielded 846 µg L^{-1} (Liu et al. 2009). A review on Taxol production by endophytic fungi reported levels of 0.4–1.0 mg L^{-1} after strain improvement (Zhou et al. 2010). While the fungus *Alternaria alternate* var. *monosporous*, isolated from the bark of *Taxus yunanensis*, can produce 227 mg L^{-1} after treatment with ultraviolet and nitrosoguanidine (Duan et al. 2008).

The epothilones were initially isolated from the broth of the soil myxobacterium *Sorangium cellulosum* (Hardt et al. 2001). They are macrolides exhibiting weak activity against rust fungi (Hardt et al. 2001). They were later recognized as microtubule-stabilizing drugs, acting similarly to Taxol (Kowalski 1997). Besides, they are 5- to 25-fold more potent than Taxol in inhibiting cell growth. Five epothilone analogs are now undergoing investigation as candidate anticancer drugs, and their preclinical studies have suggested a broad spectrum of antitumor activity, including Taxol-resistant tumor cells. With the best therapies currently available, the median survival for patients with metastatic breast cancer is only 2–3 years, and many develop resistance to taxanes or other chemotherapy compounds. Ixabepilone is an epothilone approved in October 2007 by the FDA to manage aggressive metastatic or locally progressive breast cancer, which no longer responded to existing chemotherapies (Goodin 2008). In tumor cells, p-glycoprotein decreases intracellular antitumor drug concentrations, limiting access of chemotherapeutic substrates to the site of action. The epothilones are attractive because they are effective against p-glycoprotein-producing tumors and have good solubility in microbial drugs (Goodin et al. 2004). Chemically, epothilone B is a 16-membered polyketide macrolactone ring with a methyl thiazole group bound to the macrocycle structure by an olefinic bond. Five extra epothilones,

including patupilone (for ovarian cancer) and sagopilone, are in clinical trials.

Zhang et al. (2019a) found that epothilones glycosylation reduces toxicity and positively influences their pharmacological properties. The glycosyltransferase, responsible for amino acid modification at the epothilone catalytic activity, has been identified. Two amino acids (Q66 and P779) are essential for epothilone glycosylation efficiency. As a result of this variation, there is a reduction in epothilone toxicity, as judged by the higher glucose uptake observed in cancer cells than normal ones.

Romidepsin (Istodax, NSC630176, FR 901,228, FK228), a depsipeptide with antitumor activity, is produced by the Gram-negative *Chromobacterium violaceum* (VanderMolen et al. 2011). This compound acts by inhibiting histone deacetylase. In 2002, after NCI confirmed its antitumor activity, Fujisawa Pharmaceutical Co. (now Astellas Pharma Inc.) conducted clinical trials with romidepsin. The product was licensed to Gloucester Pharmaceuticals in 2004, later acquired by Celgene Corp. The FDA approved this compound in 2009 against cutaneous T-cell lymphoma (CTCL). There are around 1500 new cases annually and 500 deaths from CTCL, only in the USA. Two new romidepsin derivatives (romipeptides A and B), with antitumor activity against three human cancer cell lines (SW620, HL60, and A549), were isolated from *C. violaceum* (Xiong et al. 2019).

Romidepsin has also shown good activity against testicular cancer. This effect is the most frequent cancer in men between the ages of 14 and 44 years, and its incidence is increasing worldwide. Most testicular neoplasms are germ cell tumors, relatively scarce carcinomas, accounting for only 1.0% of all male malignancies. Remarkable progress has been made in advanced testicular cancer medical treatment, with a substantial increase of five years of survival value from < 30% to approximately 95%. Further, for patients initially diagnosed with stage I development, the cancer-specific survival rate at 15 years is > 99%. The cure proportion is the highest of any solid tumor, and improved survival is primarily due to the progress in understanding this disease.

The testicular germ cell tumors generally are treated with high cure rates by orchiectomy and chemotherapy. The exceptions are in the situation of patients with metastasis or with resistance to standard therapy. Romidepsin induces apoptosis and blocks the cell cycle without affecting the fibroblasts of Sertoli cells. It upregulates the NADPH-dependent dehydrogenase/reductase DHRS2 and the creatine kinase CKB genes involved in cellular energy homeostasis. Interestingly, combining romidepsin with dexamethasone may improve the treatment (Nettersheim et al. 2019). Otherwise, this compound has been considered for viral reactivation to kill latently HIV-infected cells with antiretroviral

therapy to prevent the spread of the infection (Søgaard et al. 2015).

Carfilzomid is an anticancer drug isolated from actinobacteria. Chemically, it is a tetrapeptide epoxy-ketone analog of epoxomicin. The FDA approved this compound in 2012 as an agent against multiple myeloma, and Onyx Pharmaceuticals markets the drug as Kyprolis™. Carfilzomib covalently binds and inhibits the chymotrypsin-like activity of the 20S proteasome. This inhibition results in a build-up of poly-ubiquitinated proteins, which may cause cell cycle arrest, apoptosis, and inhibition of tumor growth (Park et al. 2019).

In the fight against many cancer types, traditional cytotoxic chemotherapy has started to be replaced by targeted molecular therapies to the extent that our understanding of tumor biology has become more sophisticated. This shift has mainly changed adverse effects to a diverse range of organ systems than those seen with cytotoxic chemotherapy. Among these kinds of microbial-derived anticancer drugs, we can cite everolimus, recently approved by the FDA. Chemically, it is a 40-O-(2-hydroxyethyl) derivative of the macrolide sirolimus. Novartis markets it under the trade names Afinitor, Zortress, and Certican. The FDA approved it in 2011 to treat progressive pancreatic neuroendocrine tumors, advanced renal cell cancer, and breast cancer. Later in 2012, it was approved to treat renal angiomyolipomas complexed with tuberous sclerosis and to treat hormone receptor-positive, HER2-negative breast cancer. It binds to the FK506 binding protein-12, forming a complex that inhibits the mammalian target of rapamycin (mTOR), inducing cell growth arrest and apoptosis by blocking the progression of cells from G1 into the S phase (Lombard-Bohas et al. 2015). Besides, it is currently used as an immunosuppressant to prevent the rejection of organ transplants.

Anticancer drugs in clinical trials

The current panorama of new drugs of microbial origin with anticancer properties looks bright. Molecules with cytotoxic effects on a target (or multiple targets) with null or low toxic side effects are frequently discovered (Law et al. 2020). Elsamitrucine (elsamicin A), produced by an unidentified actinobacterium (strain J 907–21), is an example of new drugs in clinical trials. This compound inhibits the topoisomerase II and binds to DNA (Portugal 2003). An additional drug is Brostallicin, isolated from *Streptomyces distallicus*. This α-bromoacryloyl derivative of distamycin A binds non-covalently to the minor groove of DNA (Broggini et al. 2004). Brostallicin displays antitumor activity against soft tissue sarcoma and dramatically reduces the in vitro myelotoxicity in human hematopoietic cells.

Another promising drug is the polyketide geldanamycin, obtained from *Streptomyces hygroscopicus*. This compound inhibits the Heat Shock Protein 90, a chaperone protein (Bisht et al. 2003).

Further actions in search of anticancer compounds involved mining gene cluster information in tandem with nuclear magnetic resonance-based structure data. This approach allowed the isolation of the polyketide neaumycin B, a potent inhibitor of the glioblastoma cell line U87. This compound is produced by *Micromonospora* CNY-010 (Kim et al. 2018). Besides, two additional novel depsipeptides, P11A (50) and P11B (51), isolated from *Streptomyces* sp. P11-23B also exhibited strong cytotoxic activity against several human glioblastoma cell lines (U251, U87-MG, SHG-44, and C6) (Ye et al. 2017). Furthermore, two new alkaloids (geranylpyrrol A and piericidin F) with cytotoxic activity were discovered in a reedsmycins knockout mutant of *Streptomyces* sp. CHQ-64 (Han et al. 2017). Among them, piericidin F displayed the more potent anti-proliferative activity against HeLa, human lung carcinoma (A549 and H1975), and human acute promyelocytic leukemia cell lines (NB4).

Marine microorganisms have great potential for discovering new entities that can aid in the prevention and treatment of cancer. Among these microorganisms, actinobacteria have shown extraordinary proficiency in the generation of anticancer compounds. Novel anticancer compounds with IC_{50} values ranging from ng to mg include lucentamycins A-D. These compounds, isolated from *Nocardiopsis lucentensis*, are 3-methyl-4-ethylideneproline-containing peptides with in vitro cytotoxicity against the human colon carcinoma lineage HCT-116 (Cho et al. 2007). An additional drug isolated from *Micromonospora marina* is a depsipeptide named thiocoraline. This drug shows in vitro cytotoxic activity against the human colon cancer cell lines LOVO and SW620. Biparametric flow cytometry analysis with bromodeoxyuridine/DNA supported that its cytotoxic action was mediated by an arrest in the G1 phase of the cell cycle (Lombó et al. 2006). Other antitumor compounds included trioxacarcins A-C extracted from *Streptomyces* species. They showed high anti-tumor activity against a lung cell line (Maskey et al. 2004). Mansouramycins A-D isolated from *Streptomyces* sp. show activity against breast and prostate cancers (Hawas et al. 2009). The macrolide tartrolon D, from *Streptomyces* sp. MDG-04–17-069, exhibits cytotoxicity against lung, colon, and breast cancer cell lines. Salinosporamide is another remarkable anticancer compound produced by a marine actinobacterium. It is active against lung, promyelocytic leukemia, hepatocellular carcinoma, and breast cancer cell lines (Fenical et al. 2009).

More recent discoveries included the polyene macrolactam, FW05328-1 (Santos et al. 2020), isolated *from Micromonospora* sp. FIM05328. It shows potent activity against esophageal squamous cell carcinoma cell lines KYSE30, KYSE180, and EC109 (Nie et al. 2018). Furthermore, by genetic manipulation of the *Streptomyces pactum*

SCSIO 02,999 promoters, six new polyketides, pactamides A–F, were isolated. Among them, pactamide A exhibited strong activity against the human SF-268 glioblastoma, MCF-7 breast cancer, NCI-H460 lung carcinoma, and liver HepG2 cancer cell lines (Saha et al. 2017).

Two new chromodepsipeptides, neo-actinomycin A and neo-actinomycin B, were isolated from *Streptomyces* sp. IMB094 (Wang et al. 2017c). They displayed a potent anti-proliferative effect on human colorectal and lung carcinoma cell lines HCT116 and A549, respectively. Two new macrolides, PM100117 and PM100118, were isolated from *Streptomyces caniferus* GUA-06–05-006A (Pérez et al. 2016). Both PM100117 and PM100118 show potent cytotoxic effects on cell lines of human lung carcinoma (A549), breast adenocarcinoma (MDA-MB-231), and human colorectal carcinoma (HT-29). Lin et al. (2014) reported lobophorins, H and I from a symbiotic *Streptomyces* sp. (strain 1053U.I.1a.3b) isolated from cone snails. They represent a large family of spirotetronates with antimicrobial and cytotoxic activities. Of these, lobophorin I showed potent cytotoxic activity against the human T-cell leukemia cell line CEM-TART.

Although numerous compounds have been isolated from marine actinobacteria, other marine bacterial phyla have shown to be good sources of novel bioactive molecules. An example is tetra(indol-3-yl) ethenone, a novel indol isolated from *Pseudovibrio denitrificans* BBCC725. It offers moderate cytotoxicity against human lung carcinoma A549 and mouse fibroblasts L929 cell lines (Rodrígues et al. 2017). Another compound recently reported is the novel 18-O-demethylpederin (Schleissner et al. 2017). This drug shows anti-proliferative activity against human lung carcinoma (A549), human colon (HT-29), human breast (MDA-MB-231), and human pancreas (PSN-1) adenocarcinoma cell lines.

All the examples cited above show the great potential of microorganisms as a source of anticancer drugs and reveal the extraordinary chemical diversity of their metabolism to generate novel compounds. Among them, actinobacteria proved to be the most prolific and diverse producers, supporting their great significance and contribution of natural microbial products to the pharma industry.

Immunosuppressant drugs

An individual's immune system can distinguish between native and foreign antigens and elicit a response only against the latter. In the case of a vital organ failure, or an autoimmune disease, a transplant represents an option to replace the damaged organ, possibly saving the life. However, suppressor cells, which are essential in regulating the normal immune response, will reply by rejecting the transplant. The suppression of the immune response either by drugs or radiation, which prevents grafts and transplants rejection or

controls autoimmune diseases, is termed immunosuppression. The use of immunosuppressant drugs is now a feasible option to allow organ transplants. A multidrug approach involving medications with different mechanisms of action and non-overlapping toxicity profiles is commonly used for this purpose. The global organ transplant immunosuppressant drug market capacity has grown continuously and is expected to be around $5.88 billion by 2026 [https://markets.businessinsider.com/news/stocks/organ-transplant-immunosuppressant-drugs-market-worth-5-88-billion-by-2026-grand-view-research-inc-1028617966].

Microbial compounds able to suppress the immune response have been discovered. Originally, cyclosporin A was introduced as a narrow spectrum antifungal peptide produced by aerobic fermentation by the mold, *Tolypocladium nivenum*. Cyclosporins are a family of neutral, highly lipophilic, cyclic undecapeptides containing several unusual amino acids. A nonribosomal peptide cyclosporin synthetase is responsible for their synthesis. Cyclosporin has been used in heart, liver, and kidney transplants, leading to an overwhelming achievement of the organ transplant field (Borel 2002). Global annual world sales of cyclosporin A are approximately $2 billion.

The cyclosporin mechanism is possibly related to the cytosolic protein cyclophilin (immunophilin) that binds to immunocompetent lymphocytes, particularly T-cells. This complex of cyclosporin and cyclophilin inhibits the enzyme phosphatase calcineurin, which dephosphorylates the nuclear factor of activated T-cell. Under normal circumstances, this factor is responsible for activating the transcription of interleukin-2 and, therefore, leads to T-cell inactivation. Moreover, cyclosporin can also modulate the innate immune response due to the reduction of inflammatory responses in dendritic cells, macrophages, and neutrophils. Cyclosporin acts independently of cyclophilin and calcineurin, inhibiting the mitochondrial permeability transition pore formation. Thereby, it prevents the leak of mitochondrial factors like DNA, reactive oxygen species, and phospholipids that would activate the innate immune response. Besides, cyclosporin inhibits dendritic cell maturation, and the mechanism depends on the cell type but includes damage of the cellular functions, such as antigen presentation, expression of maturation markers, and cytokine secretion. Cyclosporin affects tissue-damaging factors and pro-inflammatory cytokines in macrophages and neutrophils. This result suggests novel mechanisms by which this peptide can modulate the immune response (Liddicoat and Lavelle 2019). Although this natural product is a highly effective immunosuppressant, it may cause some adverse effects like hypertension. In this effect, cyclosporin inhibits the activity of ABCA1, which transports cholesterol to the outer leaflet of the cell membrane. Thus, it elevates the intracellular cholesterol concentration and stimulates the epithelial sodium

channel in distal nephron cells, enhancing the interaction with the activator phosphatidylinositol-4,5-bisphosphate through an increase in sodium reabsorption. However, lovastatin can hinder this effect, inhibiting cholesterol synthesis produced by cyclosporin (Zhai et al. 2019).

Sirolimus (rapamycin) and tacrolimus (FK506, Fujimycin) are key organ transplant agents produced by actinobacteria. Rapamycin lacks the nephrotoxicity effect seen with cyclosporin A and tacrolimus. Therefore, it is especially suitable for kidney transplants. Rapamycin, discovered in 1975 as a *S. hygroscopicus* product was initially proposed as an antifungal drug. However, this application was discarded after finding its potent immunosuppressive and antiproliferative properties. In addition to these effects, rapamycin also exhibits antitumor, neuroprotective, and anti-aging properties. The FK506-binding protein (FKBP12) interacts with the rapamycin-binding domain by connecting to the immunophilin and inactivating the serine-threonine kinase mTOR (Hausch et al. 2013). The latter is a nutrient-sensing regulator that mediates cellular response to nutrient availability by acting at the cellular and organismic levels and is implicated in cellular processes such as autophagy, cell growth, and proliferation (Lee et al. 2018). Rapamycin also activates the lysosomal Ca^{2+} channel TRPML1 (transient receptor potential channel mucolipin 1). By activating the EB transcription factor (TFEB), TRPML1 increases autophagy and lysosomal biogenesis (Zhang et al. 2019b). In this way, rapamycin contributes to the in vivo neuro protecting and anti-aging effects.

The results in animal models suggest that rapamycin has a beneficial effect during the aging process and has therapeutic effects in Alzheimer´s disease (Kaeberlein and Galvan 2019). Roos and Murthy (2019) reported on the treatment of thyroid eye disease suggesting that a combination of sirolimus and prednisolone immunosuppressant therapy may be useful. This effect is probably due to the anti-fibroblast effects of rapamycin (Roos and Murthy 2019). In conjunction with coronary stents, the rapamycin antiproliferative effect has also been used to prevent restenosis, which typically occurs after the treatment of coronary artery disease by balloon angioplasty. A rapamycin-eluting coronary stent is sold under the trade name Cypher™.

Park et al. (2010) reviewed the biosynthesis, regulation, and mutagenic improvement of rapamycin biosynthesis. Likewise, for strain improvement of rapamycin production by *Streptomyces hygroscopicus*, Zhu et al. (2010) considered the effect of various factors such as the carbon and nitrogen source regulation. Besides, the precursor effects of acetate, propionate, methionine, pipecolic acid, and shikimic acid. Starting with a strain producing 150 mg L^{-1}, a mutant resistant to lysine inhibition yielded 260 mg L^{-1}. Further mutation to high glucose resistance generated a strain making 350 mg L^{-1}. Mutations to high shikimate concentrations

and auxotrophy to tryptophan and phenylalanine resulted in 450 mg L^{-1}. Fed-batch fermentation with glycerol and potassium phosphate supplementation yielded 812 mg L^{-1}.

In the rapamycin-producing *S. hygroscopicus*, two genes of its biosynthetic cluster, i.e., *rap G* and *rap H*, encode for positive regulatory proteins production (Kuščer et al. 2007). Overexpression of either gene increases rapamycin formation, whereas their deletions eliminate rapamycin biosynthesis. They act by affecting the operon promoter.

Rapamycin exhibits antitumor activity due to angiogenesis interference and apoptosis induction (Brown et al. 2003; Guba et al. 2002). This finding was considered advantageous to further chemically modify this compound to produce relevant derivatives such as temsirolimus (CCI-779; ToriselTM) and everolimus (RAD001). The FDA approved temsirolimus and everolimus in 2007 and 2019 for renal cell carcinoma. Novartis market everolimus under the name of Afinitor™, and the 2019 net sales amounted to $1,519 Million (https://www.novartis.com). Torisel™ has been relatively successful in the renal carcinoma market and may have significant generic loss with patents expiring in August 2019 (US), February 2020 (Japan), and March 2020 (EU) [https://pharmastore.informa.com/product/torisel/].

The low aqueous solubility of rapamycin has been amended in its analogs everolimus, temsirolimus, and AP23573. Everolimus (marketed as Certican) is currently used as an immunosuppressant to avoid the rejection of organ transplants. Novartis sold it under the tradenames ZortressTM (USA), CerticanTM (Europe and other countries) in transplantation medicine, and AfinitorTM in oncology. Everolimus likely has a role in heart transplantation by inhibiting cardiac allograft vasculopathy progression (Gude et al. 2017). In 2010, phase III trials in gastric cancer, hepatocellular carcinoma, and lymphoma were underway [http://www.genengnews.com/gen-news-highlights/novartis-afinitor-cleared-by-fda-for-treating-sega-tumors-in-tuberoussclerosis/81244159/]. However, this drug did not noticeably improve the overall survival for advanced gastric cancer that had progressed after one or two lines of previous systemic chemotherapy (Ohtsu et al. 2013). Everolimus is also used in drug-eluting coronary stents as an immunosuppressant to prevent rejection. Deforolimus (AP23573; MK-8669) or ridaforolimus is a non-prodrug rapamycin analog with nonlinear pharmacokinetic behavior. It has anti-proliferative activity against several human tumor cell lines in vitro and experimental tumors in vivo (Dancey 2006; Chen 2007). Although Ariad Pharmaceuticals and Merck announced the success of phase III trials in patients with metastatic soft-tissue or bone sarcomas, the FDA rejected the New Drug Application (NDA) for ridaforolimus in 2011. Later, in 2012, the European Medicines Agency (EMA) notified Merck of the decision to withdraw the Marketing Authorization Application (MAA) for ridaforolimus [https://newdrugapprovals.

org/tag/ridaforolimus/]. The withdrawal of the EMA application of ridaforolimus did not change Merck's commitment to the ongoing clinical trials with this compound.

Tacrolimus (FK-506) was discovered in 1987 as a fermentation product of *Streptomyces tsukubaensis*. It has approximately 100 times more immunosuppressive activity than cyclosporin A (Wen 2020). Initially developed by Fujisawa Pharmaceutical was approved by the FDA in 1994 as an immunosuppressant in liver transplantation (Yamashita 2013). Tacrolimus is marketed by several companies, including GlaxoSmithKline Plc, Abbott Laboratories, Novartis International AG, Mylan N.V., Astellas Pharma, Inc., Takeda Pharmaceuticals Company Ltd, Senju Pharmaceutical Co. Ltd., Guike Pharmaceutical Co. Ltd., DR. Reddy's Laboratories Ltd., Glenmark Pharmaceuticals Ltd., and Veloxis Pharmaceuticals. This last company sells the drug as Envarsus XR™ with a 2019 market of $1.7 billion only in the USA [https://www.jefferies.com/CMSFiles/Jefferies.com/files/Veloxis%20Pharmaceuticals%20As.pdf]. Its use has been extended to embrace bone marrow, cornea, heart, intestines, kidney, lung, pancreas, trachea, small bowel, skin, and limb transplants. Topically, it is used against atopic dermatitis, a widespread skin disease, psoriasis, and pruritus. In ophthalmology, tacrolimus was used to treat Sjögren's syndrome, allergic conjunctivitis, and dry eye disease.

In the laboratory, tacrolimus inhibits the mixed lymphocyte reaction, the formation of interleukin-2 by T lymphocytes, and the development of cytokines, including interleukin-3 and interferon-gamma. Tacrolimus has recently been shown to inhibit tumor growth factor β-induced signaling and collagen synthesis in human pulmonary fibroblast cells. This factor plays a crucial role in tissue fibrosis, including pulmonary fibrosis, treated with bleomycin. However, its use in the acute inflammatory phase may aggravate lung injury (Nagano et al. 2006). Besides, the effect of tacrolimus as an antagonist of the cold-activated cationic channel TRPM8 has also been addressed. This effect depends on a mechanism independent of its canonical signaling pathway. This channel activates a thermoreceptor involved in the sensation of cold and engages in the tearing and blinking mechanism, in itch relief, and pathologies like migraine, highlighting its therapeutic implications. On the other hand, in the study of this ionic channel's functional activity, tacrolimus could be helpful as an experimental tool (Arcas et al. 2019).

Conclusions and future perspectives

Microorganisms have contributed significantly for about 150 years to the progress of medicine and agriculture. Drugs like statins are available to treat atherosclerosis, and the panorama for new anticancer drugs of microbial origin looks bright, with marine microorganisms playing a crucial role.

Besides, the use of microbial immunosuppressant medicines is now a feasible option to allow organ transplants. Viral diseases are continuously emerging and widely spreading, especially those concerned with respiratory conditions, mainly caused by different coronaviruses. Fortunately, new drugs like protease inhibitors, terpenes, polysaccharides, polyketides, and peptides, capable of inhibiting RNA and DNA viruses, are emerging to treat these viral infections. Likely, the most critical usage of secondary metabolites has been as anti-infective drugs for bacterial and fungal diseases. However, microbes have become resistant to many antibiotics due to different factors, resulting in a risky situation, that underlines the need for new antibiotics. Unfortunately, most prominent pharmaceutical companies have aborted the search for novel antimicrobial compounds. Economic considerations have led to the decision to work on drugs active against chronic diseases, which offer higher revenues than antimicrobial agents. The length of antibiotics treatment is short and is likely to be limited by the government. Some small pharmaceutical and biotechnology companies, as well as some universities, are still developing antibiotics. Even so, most of them depend on venture capital rather than sales income, and with the present regulations, they face enormous barriers to entering the market. International agencies like the FDA raised these barriers with the best purpose of ensuring public safety. Yet, they have the opposite effect, i.e., impeding antibiotic development while resistance increases (Livermore 2004). However, there are some new bright possibilities (Sanchez and Demain 2017a, b). One of the most promising is the use of uncultured microorganisms. Considering that 99% of bacteria and 95% of fungi have not been cultivated in the laboratory, efforts into finding methods to grow such uncultured microorganisms are proceeding and succeeding (Kaeberlein et al. 2002).

Screening microbes in non-conventional sources to look for new and more effective compounds represent an additional possibility. These sources included arid soils, caves, hot springs, high salinity areas or oceans, and seas (Demain et al. 2019). Furthermore, scientists are now extracting microbial DNA from soil samples, cloning large fragments into, for example, bacterial artificial chromosomes, expressing them in a host bacterium, and screening the library for new antibiotics. This metagenomics approach could open up the exciting possibility of having a large untapped pool to discover new MPs (Trindade et al. 2015; Kowalchuk et al. 2007). Another exciting possibility is genome mining (Scheffler et al. 2013; Martínez-Klimova et al. 2017), which opens the possibility to uncover the expression of certain secondary metabolites produced only under specific circumstances. Thus, eliciting cryptic clusters becomes a significant challenge under laboratory conditions, and alternative methodologies need to be sought. In addition to these three relatively new techniques, the traditional chemical

and biological modification of antibiotics could still provide novel and potent drugs. These remarks also apply to non-antibiotics such as antitumor agents and other microbial products.

MPs must continue to be explored for desirable therapeutic effects. We trust that significant progress in identifying novel antibiotics, oncology therapeutics, and other useful medicines will be made, probably not by the big pharmaceutical companies but by small research groups from institutes and universities worldwide.

Data availability All data generated or analyzed in this study are included in the present review.

Declarations

Ethics approval This review article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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