Nature's Drugs Repositories: Myxobacteria and Actinomycetes as sources of novel antiviral agents against respiratory viruses - Coronavirus, Respiratory Syncytial virus and Influenza virus

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Submitted: 4th Nov., 2025; Accepted: 25th Feb., 2026; Published online: 28th Feb., 2026
DOI: https://doi.org/10.54117/jcbr.v6i1.1
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Abstract

The respiratory viruses, respiratory syncytial virus (RSV), the influenza viruses (IV) and the coronaviruses (CoVs) have contributed remarkably to the global mortality profile, with a member of the coronavirus family, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infecting over 8 million individuals globally. Emergence of the COVID-19 pandemic has set the course for research into the discovery and development of antiviral agents against these respiratory viruses. Several sources of antiviral therapy ranging from synthetic compounds, biomolecules and natural agents from plants, animals and humans are currently being considered, explored and tested for effective and efficient health therapy. In this review, we call attention to the discovery, development and deployment of bioactive agents from microbial sources, especially those from the Myxobacteria (MXB) and Actinomycetes (ATC) families. MXB and ATC are classes of bacteria microorganisms that largely specialize in producing bioactive substances. An appreciable variety of bioactive compounds sourced from these interesting microbes have been licensed and shown to demonstrate some remarkable biological activity against bacteria, viruses, fungi, parasites, tumors, among others. There are yet untapped bioactive metabolites that reside in these microbes that possess potential for antiviral activity against these respiratory viruses. Herein we discuss some of them with the aim of guiding fellow researchers into novel routes for discovery and development of antiviral agents against these respiratory viruses.

Keywords: Myxobacteria, Actinomycetes, Antiviral, Coronavirus, Respiratory syncytial virus, Influenza virus.

Introduction

In recent years, microbial species relating to Myxobacteria (MXB) and Actinomycetes (ATC) have demonstrated outstanding ability to synthesize structurally diverse bioactive secondary metabolites (Selin *et al*., 2021; Saggu *et al*., 2023). These secondary metabolites have found wide application in development of therapeutic agents as antivirals, antifungals and antibacterials against several infectious diseases that

burden humans and animals (Muller and Gerth, 2006; Harvey *et al*., 2015; Mohr, 2018, Genilloud, 2018; Saha, 2024). Some of these metabolites possess a broad-spectrum activity while others are selective in action against specific infectious agents from viral, bacterial or fungal origin (Weissman and Mueller, 2010; Hoffmann *et al*., 2018; Mohr, 2018; Genilloud, 2018; Saha, 2024). There has been an increasing trend of antimicrobial resistance to some of these secondary metabolites serving as antibiotics, which has led to intense search for better therapeutic agents of microbial origin with not just palliative effects but ultimately, a curative effect. In view of the emergence of new infectious disease outbreaks, relying upon the instrumentality of these bioactive secondary metabolites as antimicrobial agents to curb or cure these emerging infectious diseases could be promising, and therefore intensifying research into discovering more of these potentially bioactive agents should be a worthy task to pursue.

In this review, we focused on the potential antiviral agents from the MXB and ATC against coronaviruses (CoVs), respiratory syncytial virus (RSV) and influenza virus (IV), with the aim of creating awareness to the degree of interest and volume of work that has been done with respect to this area of research. We hope that this will guide fellow researchers on the direction of research to follow regarding antivirals from microbial species related to MXB and ATC.

Nature's drugs repositories

Myxobacteria (MXB)

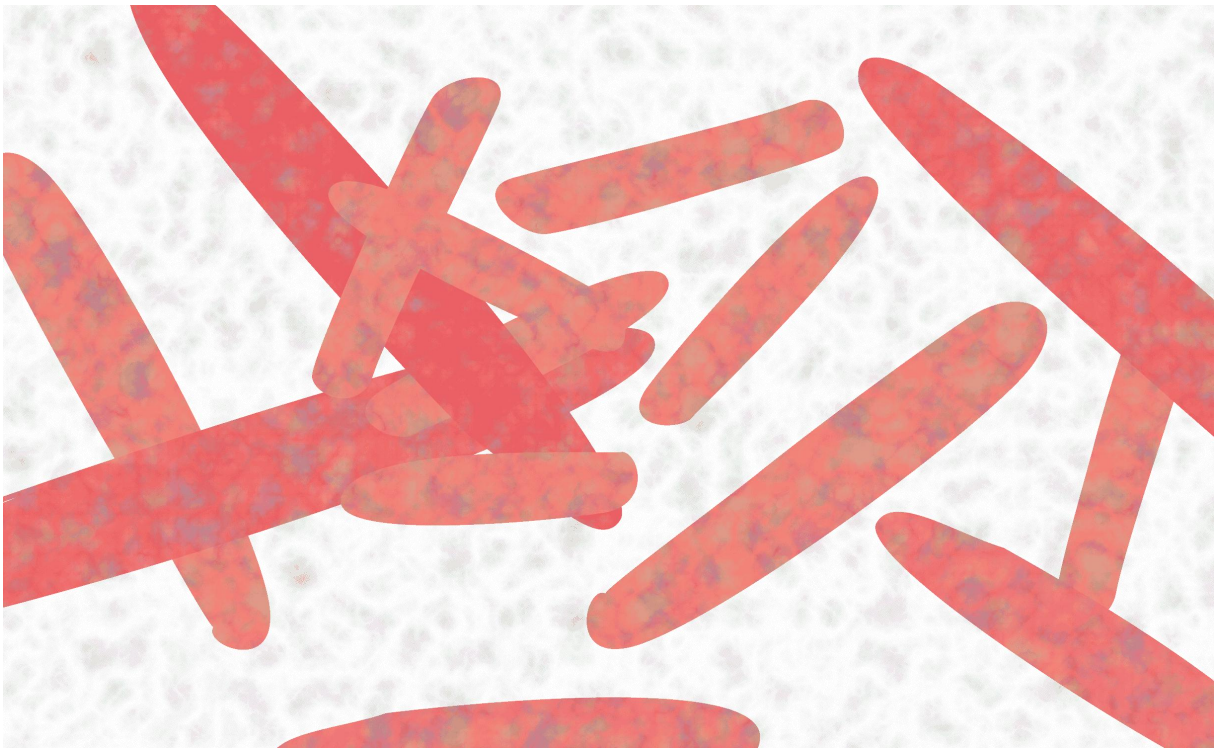


Fig 1. Schematic representation of *Myxococcus Xanthus*

MXB are organisms that belong to the order Myxococcales, within the class δ-proteobacteria (Schneiker *et al*., 2007; Liu *et al*., 2019; Bhat *et al*., 2021). They are rod-shaped, Gram-negative bacteria that are generally found in natural environments (Fig. 1), especially in places that are teeming with abundance of organic matter and microbes (Weissman and Müller, 2010; Zhang *et al*., 2013; (Zou *et al*., 2024). They have been isolated from a variety of habitats such as soil, bark of trees, plants, oceans, freshwater lakes, and animal dung (Mulwa and Stadler, 2018; Li *et al.,* 2024; Zou *et al*., 2024). They are divided into two groups; the cellulose-decomposers and micro-predators. The micro-predators are able to lyse other living microbial cells by secreting several forms of lyases deleterious to those cells; interestingly, there is no known MXB that is pathogenic to humans (Reichenbach, 2001; Sydney *et al*., 2021). In recent times, over 100 novel carbon skeleton metabolites and over 600 derivatives have been identified from thousands of MXB strains (Liu *et al*., 2019; Saggu *et al*., 2023). These metabolites include polyketides, non-ribosomal peptides and their hybrids, indoles, glycosides,

lactones, amides, to mention but a few, which demonstrate remarkable cytotoxic, antibacterial, antifungal, antiviral, immunomodulatory, and antioxidative activities with varying modes of action (Herrmann *et al*., 2016; Hoffmann *et al* 2016; Mohr, 2018; Wang et al., 2024; Zang et al., 2024)..In addition, MXB possesses umpteen genetic variations with genes coding for secondary metabolites in its relatively large genome; this have informed their use as promising sources for diverse novel bioactive metabolites (Liu *et al*., 2019; Saggu *et al*., 2023)**.** It was also reported that some MXB produce diverse carotenoids, lyse pathogenic bacteria and fungi, degrade 2-chlorophenol, and reduce uranium (VI); hence, demonstrating that they possess potentials for wide applications in agriculture, biomedicine, chemical industry, and environmental protection (Mohr, 2018; Liu *et al*., 2019; Bhat *et al*., 2021; Saggu *et al*., 2023; Zhang *et al*., 2024). However, challenges associated with the isolation, purification, and cultivation of MXB abound, and better strategies for efficient isolation and cultivation of both pre-discovered strains and novel taxa are evolving.

Actinomycetes (ATC)

ATC are gram-positive bacteria that morphologically resemble fungi because of their elongated cells that branch into filaments or hyphae (Berezin *et al*., 2019; De Simeis & Serra, 2021). The hyphae of the ATC are much smaller than fungal hyphae; this way they are distinguished from fungal hyphae. They are isolated and cultivated from soil and marine samples. Majority of ATC live in extreme environments, such as saline soil and saltwater (Pepper and Gentry, 2015; Singh *et al*., 2016; Kim, 2021). ATC are generally recognized as the chief source of most microbially derived bioactive compounds employed as therapeutic interventions for several infectious diseases (Genilloud, 2018) with majority of them originating from the genus, *Streptomyces* (Jakubiec-Krzesniak *et al*., 2018). Most of these bioactive compounds that served as antibiotics, antitumor agents, enzymes, and immunosuppressive agents, were majorly isolated from terrestrial ATC (Arasu *et al*., 2016). In most recent times, ATC recovered from marine and hyperhalophilic unexplored soil regions have attracted much interest to researchers for application in biomedicine (Gorajana *et al*., 2007; Sarkar & Suthindhiran, 2022; Xu et al., 2024). Novel secondary metabolites from these halophilic ATC have been reported to demonstrate antibacterial, antifungal and antiviral activities (Lee *et al*., 2007; Subramani & Aalbersberg, 2012; Zhang *et al*., 2020a;

Ibrahim *et al*., 2025); hence, they hold a promising future for the cure of infectious diseases. They have also been shown to possess antitumor, anticancer, anti-inflammatory, antioxidant, and antimalarial activities with differing modes of action (Abdel-Mageed *et al*., 2010; Ibrahim *et al.,* 2024). Thousands of antibiotics isolated from Streptomyces still represent only a small fraction of a collection of bioactive compounds that have been produced; thus, isolation of new strains of *Streptomyces* and other ATC from natural resources, and the characterization of their secondary metabolites is a promising venture (Rahman *et al*., 2011; De Simeis & Serra, 2021).

Respiratory viruses of importance

Coronaviruses

Coronaviruses (CoVs) are animal and human viruses possessing a positive-sense single-stranded RNA genome that is encapsulated within a membrane envelope and is spherical (Burell *et al*., 2017; Wang *et al*., 2020). Scattered over the surface of their viral membrane are glycoprotein spikes that give coronaviruses a crown-like posture (Liu *et al*., 2020). There are four classes of coronaviruses designated as alpha, beta, gamma, and delta. The beta-coronavirus class includes the middle-east respiratory syndrome virus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV, which is the causative agent of COVID-19) (Liu *et al*., 2020); other beta-coronaviruses include the human viruses, HCoV-OC43, HCoV-HKU1 and the prototype mouse hepatitis virus (MHV) (Burell et al., 2017). SARS-CoV-2 attacks the lower respiratory system leading to viral pneumonia; however, it may also affect the gastrointestinal system, heart, kidney, liver, and central nervous system causing multiple organ failure (Liu *et al*., 2020). Report from the coronavirus global pandemic analysis suggests that SARS-CoV-2 is more contagious than SARS-CoV as it infected over 8 million individuals and claimed over 450,000 lives globally as of June, 2020 (WHO COVID-19 dashboard) (Cascella *et al*., 2023).

Respiratory Syncytial Virus, RSV

The human RSV of the genus, *Pneumovirus*, subfamily *Pneumovirinae*, belonging to the family, *Paramyxoviridae*, exists as two antigenic subgroups (A and B) and they exhibit wide divergence in their genomic sequence (Collins *et al*., 2013; Kaler *et al*., 2023). Other members of this family include; ovine RSV (ORSV), bovine RSV (BRSV), and pneumonia virus of mice (PVM), human and avian metapneumoviruses (HMPVand

AMPV), mumps, measles, animal and human parainfluenza viruses (PIVs), Nipah and Hendra viruses (Collins *et al*., 2013). The RSV genome is a single-stranded negative-sense non-segmented RNA and its virion consists of a nucleocapsid packaged in a lipid envelope that contains three viral transmembrane surface glycoproteins derived from the host cell plasma membrane. The glycoproteins include the large glycoprotein G, the fusion protein F, and the small hydrophobic SH protein. RSV predominantly causes viral lower respiratory tract infections in infants younger than 2 years of age and the elderly. It could also affect immunocompromised adult patients (Openshaw and Tregoning, 2005; Wildenbeest *et al*., 2024)

Influenza virus

Influenza viruses belong to the family, *Orthomyxoviridae* and possess an enveloped genome consisting of segmented negative-sense single-strand RNA segments. Four main genera of this family include; types A, B, C and Thogotovirus, of which, only genera A and B are of clinical importance to humans (Nuwarda *et al*., 2021; Uyeki *et al*., 2022). Influenza A and B viruses have eight genome segments that are loosely enclosed by a nucleoprotein. Influenza A viruses, unlike Influenza B viruses, are subdivided into a number of subtypes according to the antigenic properties of their envelope proteins. Influenza A viral infection occurs in humans, pigs and horses. Replication of these viruses in their hosts majorly affects their lower respiratory tracts, which have contributed in no lesser measure to its global mortality status (Blut, 2009; Li *et al*., 2024).

Antiviral agents from myxobacteria against coronaviruses, RSV and influenza virus

Over a hundred secondary metabolites from the family of Myxobacteria, none of which have been tested for antiviral activities against the respiratory viruses in question according to available literature. Interestingly, some have been reported to have demonstrated antiviral activities against Human Immunodeficiency virus (HIV-1), Ebola virus and hepatitis-C virus (see Table 1) (Weissman and Müller, 2010; Herrmann *et al*., 2016). The Coronaviruses, Influenza virus and RSV are related to HIV, Ebola virus (EBOV) and hepatitis- C virus (HCV) in that they are all RNA viruses. Therefore, it is logical to evaluate the potential of these secondary metabolites from the Myxobacteria family as antivirals against these RNA respiratory viruses since some of the metabolites have demonstrated broad-spectrum activity. All novel

myxobacterial-derived compounds, excluding four patented metabolites isolated before 2010 were reported by Weissman and Müller (2010); some of them were reported to have demonstrated some antiviral activity against RNA viruses. More recently, Herrmann *et al*. (2016) as well as Haack and coworkers (Haack et al., 2022) reported more compounds from myxobacteria. These discoveries and their modes of action, where applicable, are shown (see Table 1).

Table 1: Some Natural Products from the myxobacteria with Antiviral Activity

Natural Products / Secondary Metabolites	Structural Class	Antiviral Activity	References
Apicularen	Benzolactone enamide	HIV-1, HCV	Weissman and Müller, 2010; Martinez et al., 2015
Archazolid	Macrolactone	HIV-1, HCV	Weissman and Müller, 2010; Martinez et al., 2015
Aetheramide	Depsipeptide	HIV-1	Herrmann et al., 2016
Crocapeptin B	Depsipeptide	HIV-1, HCV	Martinez et al., 2015
Chondramide	Depsipeptide	HIV-1, EBOV	Weissman and Müller, 2010; Herrmann et al., 2016
Disorazoles	Macrodilactone	HIV-1, HCV	Weissman and Müller, 2010; Martinez et al., 2015
Epothilones	Macrolactone	HIV-1, HCV	Herrmann et al., 2016; Martinez et al., 2015
Etnangien	Macrolactone	HIV-1	Weissman and Müller, 2010
Noricumazole	Polyketide	HIV-1, HCV, EBOV	Herrmann et al., 2016
Phenalamide	Polyene	HIV-1	Weissman and Müller, 2010
Phenoxan	Pyrone	HIV-1	Martinez, et al., 2013
Ratjadon	α-Pyrone	HIV-1	Herrmann et al., 2016; Martinez et al., 2015
Soraphens	Macrolactone	HIV-1, HCV, EBOV	Herrmann et al., 2016; Martinez, et al., 2013
Spirangien	Polyketide, spiroketal	HIV-1	Herrmann et al., 2016

Sulfangolid	Macrolactone	HIV-1	Herrmann et al., 2016
Thiangazole	Alkaloid	HIV-1	Herrmann et al., 2016
Tubulysins	Peptide	HIV-1, HCV	Weissman and Müller, 2010; Martinez et al., 2015
Thiamyxin A	Peptide-Polyketide	Coronavirus	Haack et al., 2022
Thiamyxin B	Peptide-Polyketide	Coronavirus, Zika virus, Dengue virus	Haack et al., 2022
Thiamyxin C	Peptide-Polyketide	Coronavirus, Zika virus, Dengue virus	Haack et al., 2022
Thiamyxin D	Peptide-Polyketide	Coronavirus	Haack et al., 2022

KEY: HIV: Human immunodeficiency virus; Hepatitis C virus; EBOV: Ebola virus

Furthermore, four out of the 154 myxobacterial derived compounds screened for anti-HIV activity, including Sulfangolid C, Soraphen F, Epothilon D and Spirangien B exhibited the best anti-HIV activity with good safety profile. They all showed EC_{50} values in nano-molar range with selectivity index, SI > 15 (Martinez, *et al*., 2013). The same study observed that there were several overlaps when compared with a previous screening conducted for Hepatitis C virus (HCV) using the same library. One of the four active compounds mentioned above, Spirangien B, has been shown to inhibit IkBα, the major regulator of the NF-κB signaling pathway (Reboll *et al*., 2012). Repression of IkBα has been reported to facilitate the inhibition of viral replication in Jurkat cells (Reboll *et al*., 2012). Also, Soraphens are inhibitors of acetyl-CoA carboxylase (Jump *et al*., 2011). It was postulated that Soraphens may inhibit infectivity of viruses that require fatty acids for replication as the enzyme, acetyl-CoA carboxylase (Fig. 2), is required for elongation of fatty acids (Raveh *et al*., 2013). However, a class of Soraphens, namely soraphen A, was reported to inhibit HIV-1 infection by interrupting binding to CD4 and membrane fusion to target cells (Fleta-Soriano *et al*., 2017). Epothilones (table 1) were reported to stabilise microtubuli of macrophages in anti-tumor studies (Mulwa and Stadler, 2018), however, its mechanism of action as an antiviral agent has not yet been clearly elucidated. Rhizopodin was reported to inhibit formation of actin filaments (microtubuli) which are essential

for virological synapse formation; this mode of action is also lethal to host cells (Mulwa and Stadler, 2018). Furthermore, tubulysins and disorazoles inhibit tubulin polymerization in humans, therefore further development of these compounds as antiviral drugs is limited (Martinez *et al*., 2015). Another study demonstrated that the myxobacteria-derived Ratjadone A, retarded HIV-1 infection *in vitro,* by blocking the Rev/CRM1-mediated nuclear export pathway. According to the study, the inhibitory activity of Ratjadone A occured 12 hours post-infection, and was specific for the Rev/CRM1-mediated nuclear export pathway. Using a drug affinity responsive target stability (DARTS) assay it was shown that Ratjadone A interrupted the formation of CRM1-Rev-NES complex by binding to CRM1 protein but not to the Rev protein (Fleta-Soriano *et al*., 2014)**.**

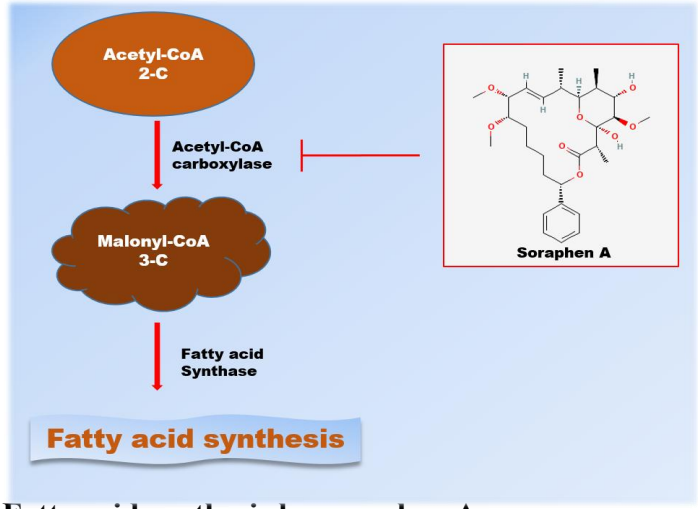


Fig 2. Inhibition of Fatty acid synthesis by soraphen A.

The challenge of some of these myxobacteria derived compounds that have demonstrated some antiviral activity has been majorly associated with toxicity, and this may be circumvented by modifying their structures for possible reduction of toxicity without diminishing efficacy (Mulwa and Stadler, 2018). Hence, there is an enormous pool of myxobacterial derived potential compounds that are yet untapped which have not been evaluated for antiviral activity against the RNA respiratory viruses considered herein. It is also noteworthy that, while the modes of action of these compounds have been reported in relation to several other biological studies, most of their modes of action have not been elucidated in relation to antiviral activity.

For instance, in anticancer studies, Archazolid and Apicularen inhibit V-ATPase function in anticancer studies leading to impaired secretion processes of matured proteases like cathepsin B, which in turn, significantly reduced invasiveness of cancer cells (Herrmann *et al*., 2016); however, their mode of action in antiviral studies have not been elucidated.

Antiviral Agents from Actinomycetes against Coronaviruses, RSV And Influenza Virus

Despite the large pool of potential bioactive metabolites derived from the Actinomycetes family, a meager amount has been evaluated for antiviral activity against Coronaviruses, RSV and Influenza viruses. Though many of them have demonstrated some antibacterial, antifungal, antiparasitic, and anticancer activities, a few have been shown to possess antiviral ability against the RNA respiratory viruses (Janardhan *et al*., 2016). Majority of them serve as lead compounds for other derived compounds which are subsequently evaluated for enhanced biological or therapeutic properties (Jakubiec-Krzesniak *et al*., 2018). We will discuss below the bioactive metabolites derived from the Actinomycetes that have so far demonstrated antiviral potentials against the respiratory viruses being considered herein.

Bioactive metabolites derived from the Actinomycetes with antiviral activity against coronaviruses have not yet been reported, although secondary metabolites from plants and fungi have been reported to demonstrate antiviral activity against them. Most recent study conducted with respect to natural products from the microbial community against SARS-CoV-2 was an *in-silico* study. Previously discovered and documented secondary metabolites from the *Aplysinidae* family, *Pterogorgia citrine,* and the *Petrosia strongylophora sp*., had their structures simulated and adapted in a molecular dynamic study involving main Protease (M^{pro}) targeting, to evaluate the potential of using microbial secondary metabolites as possible antiviral agents against COVID-19 (Zhang *et al*., 2020). However, some microbial products (Antimycin A) from the Actinomycetes have been shown to demonstrate antiviral activity against some RNA viruses including members of the Togaviridae (Venezuelan equine encephalitis virus, VEEV), Bunyaviridae (La Crosse virus, LACV), Picornaviridae (Encephalomyocarditis virus, EMCV), Rhabdoviridae (Vesicular stomatitis virus, VSV), Paramyxoviridae (Sendai virus, SeV), and Flaviviridae (Hepatitis C virus, HCV) families (Jakubiec-Krzesniak *et al*., 2018; Raveh *et al*., 2013)**.** Viruses such as Herpes

simplex viruses (HSV-1 & 2), Porcine epidemic diarrhea virus (PEDV), HIV-1, Zika virus (ZIKV)**,** Influeuza A and B viruses, White spot syndrome virus (WSSV) (Janardhan *et al*., 2016), East equine encephalitis virus (EEEV) and the West equine encephalitis virus (WEEV) (Raveh *et al*., 2013) have shown remarkable decline in infectivity upon treatment with few bioactive metabolites from the actinomycetes (see Table 2).

Table 2: Some Natural Products from the Actinomycetes with Antiviral Activity.

Natural Products / Secondary metabolites	Bacteria Origin	Structural Class	Antiviral Activity	References
Antimycin A and its derivative (Antimycin A1a)	*Streptomyces kaviengensis*	Bis-lactone	WEEV, FMV, EMCV, VEEV, LACV, SeV, HCV	Raveh et al., 2013
Xiamycin	*Streptomyces sp.*	Sesquiterpenoids	PEDV	Jakubiec-Krzesniak et al., 2018
4862F	*Streptomyces albosporus*	Peptide	HIV-1	Liu et al., 2012
Ahmpatinin	*Streptomyces sp.*	Peptide	HIV-1	Pepper & Gentry,2015
Daptomycin	*Streptomyces roseosporus*	Lipopeptide	Zika virus	Rahman et al., 2011
Nanchangmycin	*Streptomyces nanchangensis*	Polyether	Zika virus	Rausch et al., 2017
Benzastatin C	*Streptomyces nitrosporeus*	Alkaloid	HSV-1&2, VSV	Raveh et al., 2013
SF 2487	*Actinomadura sp.*	-	IAV	Reboll et al., 2012
Crude Extract	*Streptomyces albus*	-	IAV	Reichenbach, 2001
Crude Extract	*Streptomyces avermitilis*	-	IAV	Reichenbach, 2001
Crude Extracts	Extremophilic actinomycetes	-	Influenza viruses, SeV, NDV	(Berezin et al., 2019)
Decatromicins	*Actinomadura* sp.	Polyketide	Dengue virus	Euanorasetr et al., 2019
Persicamidines A–E	*Kibdelosporangium persicum*	Terpenoids	Coronavirus	Keller et al., 2022
Huimycin	*Kutzneria albida*	Pyrrolopyrimidine	VSV	Huang et al.,

				2018; Shuai et al., 2020
Napyradiomycin	*Streptomyces kebangsaanensis*	Meroterpenoids	PRV	Zhang et al., 2023
Virantmycins D–G	*Streptomyces jiujiangensis*	Benzopyrrole, benzopyridine	PRV	Liu et al., 2023
Zelkovamycins F, G	*Streptomyces bacillaris*	Peptide	HCV	Hao et al., 2022
Neoabyssomicins F, G	*Streptomyces koyangensis*	-	VSV	Huang et al., 2018
Virantmycin B, C	*Streptomyces* sp. AM-2504	Terahydroquinoline, indoline	Dengue virus	Kimura et al., 2019
Xiamycins C-E	Streptomyces. Sp. HK18	indolosesquiterpenoids	PEDV	Kim et al., 2016
Geninthiocins E, F	*Streptomyces* sp.	cyclic thiopeptides	IAV	Fang et al., 2022
Crude extract	*Streptomyces sp. SMU 03*	-	IAV	Li et al., 2020
Dihydromaniwamycin E	*Streptomyces sp. JA74*	Maniwamycin	IAV, Coronavirus	Saito et al., 2022

KEY: WEEN: western equine encephalitis virus; EEEV: Eastern equine encephalitis virus; VEEV: Venezuelan equine encephalitis virus; FMV: Fort Morgan virus; EMCV: encephalomyocarditis virus; LACV: La Crosse virus (LACV); SeV: Sendai virus; PEDV: Porcine epidemic diarrhea virus; IAV: Influenza A virus; Pseudorabies virus; HCV: hepatitis C virus; HSV: Herpes simplex virus; HIV: Human immunodeficiency virus; VSV: Vesicular stomatitis virus.

A marine actinomycetes strain, *Streptomyces kaviengensis*, isolated from the coast of New Ireland (Papua New Guinea) was explored for a novel metabolite with antiviral activity. A metabolite was isolated and was found to be an antimycin A derivative; it was labeled antimycin A1a. Antimycin A1a demonstrated high antiviral activity against the WEEV with IC_{50} value of less than 4 nM and a relatively high selectivity index (>550). It was reported that its mode of action was associated with the interruption of the mitochondrial electron transport chain (mETC) and partly, disruption of *de novo* biosynthesis of pyrimidines.

Also,derivatives of Xiamycin and peptides isolated from actinomycetes of genus, *Streptomyces*, were reported to have demonstrated significant antiviral activity against PEDV, HIV-1 and the Zika virus (Jakubiec-Krzesniak *et al*., 2018). Again, crude extracts from the genus, *Streptomyces*, isolated from Lagos lagoon sediments were reported to demonstrate antiviral activity against Influenza virus, creating the

opportunity for further investigation into possible bioactive secondary metabolites with antiviral activity.

Moreover, while the influenza viruses have few natural products from Actinomycete that have shown any antiviral activity against them, the RSV, belonging to the paramyxovirus family, has so far no secondary metabolite of actinomycete origin reported to demonstrate antiviral activity against it. However, studies have shown that antimycin A demonstrated some antiviral activity against Sendai Virus, a member of the paramyxovirus family; it was reported to suppress replication of recombinant SeV labeled with green fluorescent protein (GFP) inoculated in both Vero and BE (2) cells (Raveh *et al*., 2013).

More recent study by Berezin *et al*., (2019), showed that crude extracts from five strains of unnamed extremophilic actinomycetes isolated from Kazakhstan ecosystems demonstrated significant antiviral activity against paramyxoviruses (Sendai Virus and Newcastle Disease Virus, NDV) and influenza viruses (strains H7N1, H5N3, H1N1 and H3N2) (Berezin *et al*., 2019). Their antiviral activity was tested by evaluating their effect on neuraminidase and hemagglutination activities of the viruses, creating the opportunity for further exploration of novel antiviral secondary metabolites from the bioactive crude extracts of these extremophilic actinomycetes.

Conclusion and recommendations

Research prospects for antiviral agents from the myxobacteria and actinomycetes seem promising, and possess enormous potential for development of antiviral agents against the RNA respiratory viruses being considered. Novel approaches for engineering these microbes to synthesize new bioactive metabolites and screening them for antiviral activity against the respiratory viruses need to be given more attention. Also, repurposing of already developed secondary metabolites for antiviral activity against the respiratory viruses are worth considering, while efforts to investigate structure-function relationship need to be intensified; useful structural modifications could be explored to develop more effective and safe antiviral agents against the respiratory viruses. Furthermore, *in vivo* studies could be employed to further establish antiviral activity; hence, there is need to develop suitable humanized-animal models for evaluating the antiviral activity of the novel secondary metabolites from these microbes against these threatening RNA respiratory viruses aforementioned.

Declaration of conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this manuscript.

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