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Secondary antiviral metabolites from fungi with special reference to coronaviruses

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Abstract: Profound inspection of the life forms on the earth teaches how to be the complexity of interrelationships among the various systems. Because of the emergence of novel viruses all the time and the inadequate of vaccines and antivirals, viral contagions are amongst the most causative diseases affecting people worldwide. Fungi exemplify a massive source of bioactive molecules as, many fungal secondary metabolities like Oxoglyantrypine, Carneic acid F, Scedapin C, Asteltoxin E, Phomanolide, Norquinadoline A and Quinadoline B have antiviral activity. This review deals with how secondary metabolites of fungi can help in the war against viruses in general and especially Coronaviruses moreover several pieces of literature pointed out that many clusters of fungi in different biotopes are waiting to be exploited.

Introduction

Biological sciences have accomplished enormous discoveries in numerous arenas. Microorganisms are one of them, despite this, viruses as unique creatures, however, still have several aspects to be discovered. One of the main mystery aspects is how to stop infectious viruses. Recently, unknown pneumonia was reported and rapidly spread around the world, leading to a unique pandemic. The newly emerged coronavirus disease 2019 (COVID-19) rapidly outspread as a challenge worldwide and now is one of the biggest infectious pandemics in human society (Spinelli and Pellino, 2020). The causative agent was soon revealed and identified by the World Health Organization as a 2019 novel coronavirus. The virus causes severe acute respiratory syndrome and causes direct tissue damage; furthermore, it can lead to extrapulmonary manifestations by affecting the endothelium, evoking thrombosis, dysregulating the immune responses, and causing the incompatibility of the pathways related to angiotensin-converting enzyme 2, with additional complications on the other organs (Ebrahimi *et al.*, 2021; Gupta *et al.*, 2020).

Antibiotics have been playing a vital role in the near past of human history by preventing the outbreak of various killing pandemics and fighting several diseases, such as urinary tract infections, strep throat, whooping cough, and life-threatening illnesses like sepsis generated by other microorganisms. On the other side, antibiotics can, unfortunately, have serious side effects and lead to antibiotic resistance, where the microorganism cannot be stopped by the antibiotic, representing a grave global problem. Therefore, the golden advice is not to consume an antibiotic unless needed. The

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matter here is that viruses, like the common cold, the flu, or the recently appeared COVID-19, cannot be inactive by antibiotics. That, in turn, urged to search for efficient alternatives antiviral drugs to deal with viral diseases (Murphy *et al.*, 2012). Another effective and promising approach is the utilization of fungal secondary metabolites (FSMs). FsMs are small organic molecules (less than 4 kDa) not involved in cell growth and development but have a pivotal role in self-defense, niche adaptation, and communication with the environment. These compounds were reported to have various uses not only in medicines and recreational drugs as antiviral properties but also in vast applications worldwide as flavorings and pigments (Murphy *et al.*, 2012).

Viruses; our friends and enemies

Viruses are the smallest microscopic obligate intracellular parasites, generally much smaller than bacteria. There is a controversial disagreement between biologists; many consider viruses to be non-living as they lack a cellular structure (only protein coating surrounding genetic material) and cannot metabolize by themselves, rather they lack the ability to thrive and duplicate outside a host cell, requiring a host cell to replicate and create new units. Some other scientists hold that viruses can be considered organisms because they have genomic material (DNA or RNA) and can employ the metabolism of their host to make copies of themselves to regenerate. Nanoparticles are another name that could be applied to viruses (Marintcheva, 2018; Murphy *et al.*, 2012). Harmonically, they can be considered as living nanoparticles based on their unique way of reproduction, which is performed through three main steps; (1) the initiation of cell infection by the viral genome, followed by (2) the replication and expression of the viral genome, and finally (3) the release of progeny from infected cells. This unique mechanism argues for special treatment that differs from those applied to other microorganisms. Accordingly, their treatment is somehow different (Dimmock *et al.*, 2015; Marintcheva, 2018). Viruses are a genuine challenge to humankind. They have a reputation for being the cause of contagion and millions of human deaths all over the world. This widespread disease and death, e.g., Ebola, Swine Influenza, Avian Influenza, Dengue fever, and currently, COVID-19, have, no doubt, bolstered such reputation (Srinivasa Rao and Vazquez, 2020; Xia *et al.*, 2020). That is why finding out alternative antiviral medications represents one of the utmost important goals on the humankind level. On the far side, several benefits of viruses have been stated. For several pieces of evidence, it turns out that the virus does not necessarily mean diseases or pandemics. They are not bad at all, and some viruses might be good and required for the smooth continuation of life on Earth. Next are some examples.

Phage therapy, the next generation of drugs, involves the use of phages to treat fungal and bacterial contagions and could be a viable strategy to combat drug-resistant strains. For instance, phage treatment was applied to the aortic graft infected with *Pseudomonas aeruginosa* the patient had unrelated surgery without any side effects (Chan *et al.*, 2018). In many cases, it is possible to prompt viruses to do the job thanks to their unique ability to integrate into DNA, viruses can be used to inject genes into cells, which can reverse some genetic diseases. For example, some viruses were used to cure hemophilia, a blood disorder that prevents clotting (Nienhuis *et al.*, 2017). Recently, experiments have been successful in the lab on using oncolytic viruses to treat cancer cells and dissolve tumors (Ma *et al.*, 2020). Viruses might be crucial to the development of healthy organs. Thanks to experiments on the human microbiome, it has become obvious that virome (the set of all viruses, both eukaryotic and prokaryotic, in a given niche), is unique to each individual, and it was clear that the microbiome health is mediated by virome in the body organs such as intestines and has a lot of important roles in the intestine and immune system development (Neuman and Koren, 2017; Trastoy *et al.*, 2020). For another group of living organisms, i.e., plants, viruses can be quite devastating from the agricultural point of view, but on the other side, if it is utilized wisely, virus infection improves drought tolerance and abiotic stress of plants, which correlates with increased osmoprotectants and the levels of antioxidants in diseased plants such as *Beta vulgaris* (Xu *et al.*, 2008). Other viruses can cause desirable effects in their hosts, e.g., *Abutilon mosaic virus* enhances the aesthetics of some ornamental plants such as *Abutilon* spp. and *Hibiscus* spp. (Valverde *et al.*, 2012). However, these desirable effects are now carried out under controlled conditions.

Antivirals; challenges and difficulties

Antivirals are a class of compounds with an antimicrobial nature, either secreted by a living cell (animals, plants, fungi, bacteria, etc.) or chemically synthesized, that hinders viral duplication through interference with one or more of the viral life cycle phases (cell attachment, cell penetration, viral uncoating, viral genome replication, maturation, and viral progeny release). Antivirals represent an important therapeutic tool that complements the action of vaccine therapies in curing and hindering viral contagions (Stiver, 2003). Anyhow, there are numerous precautions and limitations that restrict the absolute application of antivirals. The curing process of viral infections has verified more obstacles because viruses are quite tiny and obligate intracellular parasites, and very specific to the host, even tissue and cell. Other viral infections are contagious with a high capability to be transmitted from one host to another such contagiousness extends for varying periods depending on the virus kind. The ease of viral transmission is another challenge. Viruses can spread through touch, saliva, air, sexual contact, sharing contaminated needles, insect vectors (mosquitoes and ticks), and finally, food and water (Dimmock *et al.*, 2015; El-Hersh *et al.*, 2013; Marintcheva, 2018).

Difficulties arise, also, when attempts are made to deal with viruses, because of the unique structural system, which does not react to the ordinary drugs (used to manage bacterial and fungal diseases) such as the ordinary antibiotics that cannot treat viral infections, fortunately, most viral illnesses could be managed by the immune system and can effectively heal the illness within 7 to 10 days (Murphy *et al.*, 2012). However, the response degree of

the immune system varies from one person to another based on several factors such as health conditions and age (Linden *et al.*, 2015). The ordinary strategy of viral treatment depends mainly on the hindering of the viral life cycle via induction of immune system response through vaccination (immunizations), utilizing the weakened virus (live or killed state), or proteins or toxins from the virus. This strategy aids the immune system to mature self-protection from a disease. Since the enlargement of the vaccines strategy, they have drastically reduced viral diseases such as polio, measles, and chickenpox (Murphy *et al.*, 2012). Besides, vaccines can protect humans from being infected with several viruses such as the flu, hepatitis A, hepatitis B, human papillomavirus, and others (Adams *et al.*, 2004; El-Hersh *et al.*, 2013; Stiver, 2003). However, the virus of human immunodeficiency (HIV), is still, another challenge to the immune system, which is easily attacked by the virus, leading to the development of acquired immunodeficiency syndrome (AIDS), till now, there is no radical medication curing HIV. Alternatively, people suffering from AIDS could use potent antiretroviral therapy to transform HIV infection into a chronic disease, such that people dealing with HIV/AIDS as a chronic disease, and have just a near-normal life expectancy close to the general population (Back and Marzolini, 2020).

For some viral diseases, such as herpes simplex virus infections (Adams *et al.*, 2004), HCV (El-Hersh *et al.*, 2013), and influenza (Stiver, 2003), antiviral medications have become available. But the use of antiviral prescriptions has been correlated with the expansion of drug-resistant viruses. Unfortunately, in some cases, the virus still survives in the nonactive form in the patients, as in the situation of HIV (Back and Marzolini, 2020). Anti-replication agents, which unravel virus and hinder viral cycles, guide the triggering of immune system response are other weapons against viruses. Such drugs can be obtained by modification of existing sources, their combinatory use, or the rediscovery of old drugs with new functions, the problem here is that several of these anti-replications remain unclear (Linden *et al.*, 2015; Said and Abdelwahab, 2013; Vigant *et al.*, 2015).

Moreover, the problems of targeting the viral proteins and/or cellular factors are the high rate at which viruses produce mutant resistant strains, and the viruses may deviate the cellular factors from their original pathway and still cause an effective infection, also, targeting cellular factors might have an antagonistic impact on the normal functioning of the host cells (Vigant *et al.*, 2015). Furthermore, the mechanisms of non-enveloped viruses to break the host cell membrane barrier are less well known, which forms an additional challenge in developing strategies against these viruses (Linden *et al.*, 2015; Said and Abdelwahab, 2013). Finally, human antivirals, including drugs and vaccines, struggle with viral infections by targeting the virus-specific factors, through the strategic dogma; one-drug for one virus (Vigant *et al.*, 2015). Consequently, only a handful of synthetic antivirals have made it past the clinical phase, especially when considering the precautions, which are required through clinical and pre-clinical trials on the antiviral drug. Of the most vital precautions, the drug should not cause any cytotoxicity, minimal side effects to the host cells, and the antiviral should be able to completely constrain the virus infection since, partial inhibition leads to the generation of drug-resistant mutants (Vigant *et al.*, 2015). Owing to these restrictions, besides the continual discoveries of new viruses, recently, the scientific communities have approved another paradigm based on one drug for multiple viruses, through targeting an essential viral function, shared in a wide-ranging of viruses i.e., the small molecules broad-spectrum antivirals (Bekerman and Einav, 2015; Bösl *et al.*, 2019; Ianevski *et al.*, 2019). The idea is to suppress and shut down the similar pathways and host factors that different viruses employ to replicate themselves inside the host cell (Bösl *et al.*, 2019; Vigant *et al.*, 2015). Hence, many questions have arisen. Are there any alternatives? If FSMs are the answer, do their effectiveness and efficacy comparable with these of ordinary antivirals? Next, these topics will be highlighted.

What are FSMs?

The necessity to find out alternative medication to viruses' infection has been arisen with the outbreak of viral diseases, as in the situation of the most recent and obvious pandemic; COVID-19, no effective drug works with such newly borne virus till now. The necessity of FSMs is in line with such an aim. Interestingly, the kingdom of fungi is representing the most miscellaneous group of microbial species, inhabiting extreme environments such as deep-sea sediments and mangrove ecosystems, moreover, the recent estimates predicting fungal species that only 3%–8% of existing fungal species are discovered and described (Hawksworth and Lücking, 2017). The United States Food and Drug Administration registered about 40% of modern drugs and 49% of new chemical products, all are based on natural products or their derivatives (Brewer, 2000). Of them, many ascomycetous species share a large proportion and have been revealed to have antiviral and other biological behaviors (Deshmukh *et al.*, 2017; Kumaresan and Suryanarayanan, 2001). Therefore, the fungal kingdom is a promising group of organisms that smoothly create a vast range of natural organic metabolic complexes.

The natural organic metabolites of fungi are categorized into primary (e.g., lignin derivatives, polysaccharides, proteins) and secondary metabolites. The latter category is usually low-molecular-weight metabolites that often have potent physiological activities; hence they are also called specialized metabolites, secondary products, or natural products (Keller *et al.*, 2005; Kumaresan and Suryanarayanan, 2001). Opposite to primary metabolites, the secondary ones share the enigmatic properties of cellular dispensability that means, the absenteeism of secondary metabolites does not result in an immediate threat to the microorganism, simply, because these compounds are not intended metabolites, rather, they are formed naturally during the ordinary life cycle of the microorganism, particularly as specific classes of related compounds secreted in a specific stage in a restricted period of the life cycle. Further, they are often restricted to a narrow set of species within a phylogenetic group (Calvo *et al.*, 2002; Yu and Keller, 2005). That is to say, only an individual or a minor group of organisms produces their own metabolite.

Obviously, as mentioned earlier, microorganisms can grow without synthesizing these metabolites, since they are not directly involved in the normal growth, development, or reproduction but, in the long-term, may cause impairment of the organism's survivability, or fecundity, or perhaps no significant change at all (Calvo *et al*., 2002; Keller *et al*., 2005). Natural sources, like fungi, have been found to be grander to combinatory chemistry for discovering novel pharmaceutical drugs that have the potential to be industrialized into new medication products. More, the biotope ecosystem varies greatly in the kind and quality of the secreted FSMs. In comparison for soil fungi, fungal endophytes, for instance, were found to have FSMs with higher and diverse biological activities. It has become commonplace to distinguish the diverse structural groups of FSMs, e.g., terpenoids, steroids, xanthones, chinones, phenols, isocumarines, benzopyranones, tetralones, cytochalasines, and enniatines (Schulz *et al*., 2002).

Among the fungal natural products, pigments are the most recognizable ingredients, which are typically brown and black pigments (melanins), giving color to spores, appressoria, sclerotia, sexual bodies, and other developmental organelles (Yu and Keller, 2005). The pigments are functioning as plant and animal virulence factors (Kimura and Tsuge, 1993; Yu and Keller, 2005) or that they are required for general survival, presumably as UV protectants (Lee and Adams, 1994), antigrowth deterrents (Scheu and Simmerling, 2004), or reactive oxygen species scavengers (Coccia *et al*., 2001). Nutritionally, the biosynthesis of FSMs depends on the growth conditions of each strain. Researchers have been applying different modifications in nutrients and physicochemical factors during fermentation processes to optimize the biosynthesis of the bioactive compounds. Fermentation processes are currently modeled and analyzed by the mathematical optimization approach, e.g., response surface methodology, which enables enhanced production of various metabolites (Al-Askar *et al*., 2018; Jakubiec-Krzesniak *et al*., 2018).

On the ecosystem level, extreme habitats such as tropical forest soil, caves, deserts, and Antarctic ecosystems are recognized as valuable sources of novel microbial metabolites of pharmacological importance (Jakubiec-Krzesniak *et al*., 2018; Sacramento *et al*., 2004). Genetically, the secretion of microbial secondary metabolites is regulated, employing gene clusters-based premise, such inherent criteria spurred efforts toward identifying the genetic factor involved in the biosynthesis process. The studies of known FSMs-biosynthetic genes reported that such genes are clustered in fungal genomes and have considerable bearing on the regulation of the secretion process. Consequently, several genome sequencings detected the genes responsible for the production of FSMs and encoded by biosynthetic gene clusters (Jakubiec-Krzesniak *et al*., 2018; Yu and Keller, 2005). The production of FSMs is driven via various pathways, their synthesis starts once the active fungal growth ceases (El-Hawary *et al*., 2017).

Table 1 shows four classes according to biochemical construction or biosynthetic origin. Polyketides represent an important category of secondary metabolites with great structural diversity from simple aromatics to highly modified complex architectures, such as macrolides, polyphenols, polyethers, polyenes, and enediynes (Luo *et al*., 2018). A promising therapeutic drug for cancers and hypoglycemia, as well as anti-influenza A virus infection, thus improving pulmonary function, without cytotoxicity. Furthermore, polyketides were reported as a potent inhibition of HIV replication (Herrmann *et al*., 2020). Nonribosomal peptides can act as anti-Zika virus activities by inhibiting RNA replication and nonstructural protein 5 production (Yuan *et al*., 2021). Terpenes are used as antivirus through maximizing the drug efficacy against different types of viruses, including the drug-resistant ones. Novel classes of terpenes can also target various sites in both the host and the virus, such as host transport machinery and/or viral polymerase (Al-Salihi and Alberti, 2021). The therapeutic indole alkaloids have

TABLE 1

Classes of the main pathway, and examples of fungal secondary metabolites

Class	Example	Fungus	Reference
Polyketides	Aflatoxin	*Aspergillus* spp.	Hanson (2008)
	Statins	*Penicillium* spp.	Gong *et al*. (2004)
	Lovastatin	*Fusarium* spp.	Demain and Fang (2000)
	Pravastatin	*Alternaria* spp.	Daley *et al*. (2017)
		Monascus ruber	Adrio and Demain (2003)
Nonribosomal peptides	Cyclosporine	*Tolypocladium niveum*	Hanson (2008)
	Penicillins		
Terpenes	Gibeberellins	*Ganoderma lucidum*	Mothana *et al*. (2003)
	Trichothecenes Carotenoids	*Ganoderma pfeifferi*	Min *et al*. (2000)
	Indole-diterpenes		Hanson (2008)
	Aristolochenes		Bohlmann and Keeling (2008)
			Schulz *et al*. (2002)
			Khanikor *et al*. (2013)
Indole alkaloids	Ergots	*Claviceps purpurea*	Peng *et al*. (2013)
	Fumigaclavines	*Aspergillus fumigates*	Daley *et al*. (2017)
	Fumitremorgens		

displayed antiviral potential against RNA viruses, including coxsackievirus A-21, equine rhinovirus, and influenza A virus. For example, the antiviral activity of arbitol against influenza virus was found to improve hemagglutinin stability, and it inhibited low-pH-induced transformation of hemagglutinin to its fusogenic state, preventing infection at the viral fusion level (Mitra *et al.*, 2021).

FSMs vs. viruses

Some important advantages characterize the natural FSMs over the chemically created antivirals, i.e., lower healing dose, lower probability of developing antiviral-resistant strains of viruses, and the multi-activity against several viruses. For example, the antiviral activity of fungal coumarin and its derivatives has been detected against a broad range of viruses such as influenza viruses, HIV, coxsackievirus A16 (CVA16), dengue virus, Enterovirus 71 (EV71), and chikungunya virus (Hassan *et al.*, 2016; Peng *et al.*, 2013). There is another advantage regarding the mechanism of action of AFSMs, i.e., the targeting of several steps in the virus life cycle. For instance, the anti-HIV targets several steps in the virus life cycle, including virus-host cell attachment, cell membrane fusion, integration, and assembly, besides the conventional targets like inhibition of the reverse transcriptase, protease, and integrase (Moore and Stevenson, 2000). Another example of the wide spectrum bioactivity of FSMs comes from the endophytic fungi, which has a huge number of bioactive compounds of pharmaceutical importance viz., antitumor, antibiotic, neuroprotective, antioxidant, anti-inflammatory, antiviral, and immunomodulatory agents, etc. (Agrawal *et al.*, 2019; Deshmukh *et al.*, 2017). Several investigations obtained promising antiviral compounds from diverse taxa of fungi; these FSMs proved to have potent activity against a wide array of viruses, confirming hope and relying on using such compounds soon. Table 2 explores some of these fungi and their FSMs.

A prospective view of FSMs vs. SARS-CoV-2

Coronaviruses belong to Nidovirales order, which contains three families (Coronaviridae, Arteriviridae, and Roniviridae), all are enveloped and measure 65–125 nm in diameter, Coronaviridae family contains two subfamilies, of which the Coronavirinae subfamily is further separated into 4 subgroups (alpha, beta, gamma, and delta coronaviruses). Phenotypically, they named coronaviruses because of the crown- or wreath-like spikes on the outer surface of the virus. Genetically, the nucleic material of coronaviruses contains a non-segmented, single-stranded, and positive-sense RNA, representing the biggest presently known RNA virus genomes, ranging from 26 to 32 kbs in the case of the Coronaviridae and Roniviridae, in contrast to Arteriviridae members, that have tinier genome (13 to 16 kbp) (de Groot *et al.*, 2011; Enjuanes *et al.*, 2008; Shereen *et al.*, 2020). Genomic assessment disclosed that the emerged respiratory coronavirus 2 (SARS-CoV-2) is phylogenetically associated with severe acute respiratory syndrome-like (SARS-like) bat viruses. The symptoms of the novel viral disease, COVID-19, include cough, fever, shortness of breath, and pneumonia (Desforges *et al.*, 2019).

COVID-19 is a significant challenge for global public health, especially because of the ease and readily transmissibility, as well as, the asymptomatic infectivity periods. The novel virus was announced in December 2019, and its outbreak has been associated with a global pandemic, early, in 2020, followed by major quarantines to prevent further spread (Shereen *et al.*, 2020; Srinivasa Rao and Vazquez, 2020). Besides being highly transmissible, the virus has a higher affinity to attach to the human Angiotensin Converting Enzyme-2 receptor, surpassing the presently known SARS-CoV and MERS-CoV infections (Zhou *et al.*, 2020), which makes the novel SARS-CoV-2 infection even more dangerous. Additionally, few broad-range antiviral medications have been assessed against COVID-19 in clinical trials, little of them, such as the

TABLE 2

Some fungal species and their antiviral secondary metabolites

Fungal species	Antiviral compound	References
Pestalotiopsis sp.	Pestalols A Transharzialactones A	Sun *et al.* (2014)
Pestalotiopsis vaccinii	Vaccinal A Vaccinol J	Wang *et al.* (2014) Wang *et al.* (2017)
Schizophyllum commune *Sclerotium rolfsii*	Curdlan Schizophyllan Scleroglucan	Zhang *et al.* (2003)
Agaricus brasiliensis *Auricularia auricula*	Sulfated polysaccharides	Cardozo *et al.* (2011) Li *et al.* (2015)
Neosartorya udagawae HDN13-313	Neosartoryadins A and B Fumiquinazoline alkaloids	Yu *et al.* (2016)
Trichoderma sp. Xy24	Trichodimerol	Zhang *et al.* (2014)
Cladosporium sp. PJX-41	Oxoglyantrypine Norquinadoline A Quinadoline B	Peng *et al.* (2013)

(Continued)

Table 2 (continued).

Fungal species	Antiviral compound	References
Aspergillus terreus Gwq-48	Isoaspulvinone E Aspulvinone E Pulvic acid	Gao *et al.* (2013)
Penicillium simplicissimum MA-332	Simpterpenoid A	Li *et al.* (2018)
Penicillium sp.	Brefeldin A	Xie *et al.* (2017)
Aspergillus sp. SCSIO 41501	Aspergillipeptides	Ma *et al.* (2013)
Cerrena unicolor	Laccase Endopolysaccharides	Mizerska-Dudka *et al.* (2015)
Cordyceps militaris *Agaricus brasiliensis* *Pleurotus abalonus* *Hericium erinaceus* *Grifola frondosa* *Flammulina velutipes* *Lentinus edodes*	Polysaccharides	Ohta *et al.* (2007) Faccin *et al.* (2007) Wang *et al.* (2012) Wang *et al.* (2019) Zhao *et al.* (2018) Ren *et al.* (2012)
Alternaria spp.	Altertoxin V	Bashyal *et al.* (2014)
Alternaria sp. ZJ-2008003	Tetrahydroaltersolanol C Alterporriol Q	Zheng *et al.* (2012)
Fusarium equiseti	Cordycepin Perlolyrine Griseoxanthone C	Hawas *et al.* (2016)
Stachybotry sp. HH1	Stachybogrisephenone B, Grisephenone A, 3,6,8-Trihydroxy-1-methylxanthine	Qin *et al.* (2015)
Neosartorya fischeri strain 1008F1	AGI-B4	Tan *et al.* (2012)
Phomopsis sp. SNB-LAP1-7–32	Carneic acid F Carneic acid O	Peyrat *et al.* (2020)
Scedosporium apiospermum 2014F41-1	Scedapin C	Huang *et al.* (2017)
Aspergillus sp. SCSIO XWS02F40	Asteltoxin E Asteltoxin F	Tian *et al.* (2016)
Phoma sp. strain YE3135	Phomanolide	Liu *et al.* (2019)
Nigrospora sp. YE3033	6-O-Demethyl-4- dehydroxyaltersolanol A 4-Dehydroxyaltersolanol A Altersolanol B Chermesinone B	Zhang *et al.* (2016)
Phomopsis sp. CGMCC No. 5416	Phomopsone A	Yang *et al.* (2020)
Truncatella angustata XSB-01–43	Truncateol P	Zhao *et al.* (2018)
Fusarium sp. L1	Fusaindoterpene B	Guo *et al.* (2020)
Colispora cavincola	Cavinafungin	Estoppey *et al.* (2017)

vaccine against SARS-CoV, can be partially effective (Shereen *et al.*, 2020). Consequently, till now, there is no clinically approved antiviral prescription or vaccine available to be used against COVID-19. These were the bad news, next are the good ones. The findings indicate that 90% of naturally occurring antibiotics and compounds including FSMs may possess antiviral capabilities (Linnakoski *et al.*, 2018), because of that the FSMs may be a gifted option.

Depending on the viral construction, SARS-CoV-2 is an enveloped virus, this feature can facilitate the antiviral activity of the FSMs. Since the existence of the envelope makes the virus sensitive to hot conditions and the acidic ecosystem (de Groot *et al.*, 2011; Enjuanes *et al.*, 2008). Fungi are already known to generate hot temperature and modify the medium to acidic conditions by their metabolites, the resultant FSMs, under these conditions, are expected to have some of the acids features of the growth medium, leading to perform better against enveloped viruses. This means that SARS-CoV-2 is expected not to be longer remain active in such conditions. Contrarily to the non-enveloped viruses, enveloped viruses cannot tolerate the environmental conditions encountered inside the gastrointestinal tract, such as bile salts, which show detergent-like action, thus can breakdown these viruses (de Groot *et al.*, 2011; Enjuanes *et al.*, 2008; Neuman and Koren, 2017). FSMs can do a similar action since many fungi have a lipolytic system that can catalyze the degradation of the lipid viral envelop like the same action occurs when treatment with lipid solvents

(Linnakoski *et al*., 2018). This mechanism is supposed to apply to the enveloped; SARS-CoV-2.

In comparison to vaccines, FSMs exemplify the ideal choice of antiviral for the treatment of COVID-19. Simply, because the development of vaccines against the newly emerging virus serotypes is a challenging and complicated process. Also, vaccination cannot help if the infection is already existing in the biological system (Linnakoski *et al*., 2018). Fungi, actually, produce several effective molecules that could also be utilized as antivirals. Many novel bioactive natural products possessing antiviral activities have already been identified as promising (Cheung *et al*., 2014; Linnakoski *et al*., 2018). So, expectations nominate FSMs, as natural products, to play a critical task in the COVID-19 treatment. FSMs have several antiviral mechanisms, for instance, viruses can be directly attacked outside cells in order to irreversibly terminate the viral particles before their attachment to cellular receptors. Another, FSMs can inhibit the receptor binding to prevent virus infection, this strategy offers a nice possibility to prevent the viral infection process (Cagno *et al*., 2018). RNA-based viruses, such as SARS-CoV-2, start their translation and transcription usually in the cytoplasm. Several antivirals of FSMs can target this infection route, acting as protectants to prevent the progress of a larger number of viral infections (Linnakoski *et al*., 2018).

To the authors' knowledge no experimental investigation was carried out to test the antiviral activity of fungal secondary metabolites, but, recently, *in silico* experiment using the computational methods, a sequence of blind and targeted molecular dockings were performed to test the inhibitory effect of endophytic fungi secondary metabolites against the COVID-19 RNA-dependent RNA polymerase. Of 99 compounds, the most five potent on the viral enzyme were predicted, and were further evaluated by both molecular dynamics simulation, and, the pharmacokinetics using the SwissADME server. Molecular docking showed that 18-methoxy cytochalasin J, (22E,24R)-stigmasta-5,7,22-trien-3-β-ol, beauvericin, dankasterone B, and pyrrocidine A compounds had the highest binding energy. The findings of molecular dynamics and SwissADME demonstrated that 18-methoxy cytochalasin J and pyrrocidine A had better effects than others in terms of protein instability, strong complex formation, and pharmacokinetic properties (Ebrahimi *et al*., 2021).

Summing up, the current knowledge of fungi as fabricators of antiviral compounds was discussed. It is probably only a matter of time before some FSMs will be clinically tested and/or approved against SARS-CoV-2. Therefore, it is significant to investigate vast groups of fungal species, as merely a small number of the known fungi have been investigated for antiviral activity. Finally, as fungi are a rich source of bioactive agents, more detailed knowledge on the antivirals from fungal metabolites is crucial, so that to develop an effective drug in order to efficiently combat SARS-CoV-2 in the near future. Also, the know-how of the bioactivity of FSMs, and their detailed targets in virus' cells must be planned to expand in the coming era.

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