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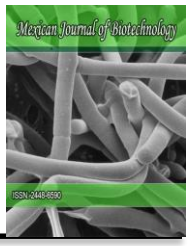

REVIEW ARTICLE

Bioactive compounds from fungi with antiviral activities: Mechanism of action and biosynthetic pathways

Compuestos bioactivos de hongos con actividades antivirales: Mecanismos de acción y rutas biosintéticas

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ABSTRACT

Viral infections have affected human health, causing critical pandemics and mortality worldwide. Viruses can also cause enormous economic problems for society globally. Bioactive compounds isolated from fungi (both edible and nonedible) have shown potential activity against viruses. In this review, we describe the fungal natural compounds that have exhibited capability to inhibit some human pathogenic viruses, such as human immunodeficiency virus, dengue virus, herpes simplex virus, bovine herpes virus, influenza virus, respiratory syndrome virus, hepatitis virus among others. We focused on the biosynthetic pathways of fungal bioactive compounds and addressed the current knowledge about their antiviral mechanisms of action and specific targets. Fungal bioactive compounds are able to inhibit viral reproduction, blocking viral penetration, replication or translation as well as integrase or protease action. Fungal compounds able to inhibit protease such as. ganodermatriol, ergosterol, terpenoids,

ganoderic acid GS-2, ganoderiol, sterigmatocystin, emericellin, cordycepin, ergosterol peroxide, myristic acid among others, may have a significant value to society at present, as they may have the potential to treat severe viral respiratory infections. Fungi represent a potential natural source of bioactive molecules that can be exploited for treating viral infections, which represent one of the main causes of disease worldwide. However, extensive investigations on clinical trials are required for the introduction of new antiviral agents into the market.

Keywords: antiviral compounds, bioactive molecules synthesis, COVID-19, fungal species.

RESUMEN

Las infecciones virales han afectado la salud humana, provocando pandemias críticas y mortalidad en todo el mundo. También puede causar enormes problemas económicos a la sociedad a nivel mundial. Los compuestos bioactivos aislados de hongos (tanto comestibles como no comestibles) han mostrado actividad potencial contra virus. En esta revisión, describimos los compuestos naturales fúngicos que han mostrado capacidad para inhibir algunos virus patógenos humanos, como el virus de la inmunodeficiencia humana, virus del dengue, virus del herpes simple, virus del herpes bovino, virus de la influenza, virus del síndrome respiratorio y virus de la hepatitis entre otros. En este documento, nos enfocamos en las vías biosintéticas de los compuestos bioactivos de hongos y abordamos el conocimiento actual sobre sus mecanismos de acción antivirales, así como el virus en el que se manifiesta la actividad antiviral. Los compuestos bioactivos fúngicos son capaces de inhibir la reproducción viral; bloqueando la penetración, replicación o traducción viral, así como la acción de la integrasa o proteasa. Los compuestos fúngicos capaces de inhibir proteasas tales como. ganodermatriol, ergosterol, terpenoides, ácido ganodérico GS-2, ganoderiol, esterigmatocistina, emericelina, cordicepina, peróxido de ergosterol, ácido mirístico, entre otros, pueden tener un valor significativo para la sociedad en la actualidad, debido a su potencial para tratar infecciones respiratorias virales graves. Los hongos representan una fuente potencial natural de moléculas bioactivas que pueden aprovecharse para el tratamiento de infecciones virales, que representan una de las principales causas de enfermedad en todo el mundo. Sin embargo, se requieren investigaciones exhaustivas sobre ensayos clínicos para la introducción de nuevos agentes antivirales en el mercado.

Palabras clave: compuestos antivirales, COVID-19, hongos. moléculas bioactivas.

1. INTRODUCTION

Human viruses are intracellular pathogens that have evolved several strategies to evade host immune responses. Therefore, viral infections are common diseases, which have long affected human health, causing illness, critical pandemics and mortality worldwide. Even mild viral infection can also cause enormous economic problems for society globally. Thus, there is a need for both vaccines and antivirals to combat viral infections. However, vaccination cannot help if the infection is already present in the system. In the

last decades, important advances on biotechnological/pharmaceutical research have allowed development of therapies for chronic diseases such as hepatitis B virus, hepatitis C virus or human immunodeficiency virus (Blair & Cox, 2016). However, the constant emergence of new viruses (or re-emergence of old ones) and their high mutation rate represent a challenge to develop new antiviral strategies to combat viral disease with new antiviral compounds.

A virion, or viral particle, is a fully assembled infectious virus that consists of a genome (DNA or RNA) packaged within a protein coat, the capsid, which functions as a shell to protect the viral genome from nucleases and which during infection attaches the virion to specific receptors exposed on the prospective host cell. The capsid may or may not be surrounded by a membrane envelope. DNA viruses can be linear-stranded or double-stranded with linear or circular genome. The entire genome may occupy either one nucleic acid molecule (monopartite genome) or several nucleic acid segments (multipartite genome). The different types of genome require different replication strategies. The genomic RNA strand of single-stranded RNA viruses is called sense (positive sense, + sense) in orientation if it can serve as mRNA, and antisense (negative sense, - sense) if a complementary strand synthesized by a viral RNA transcriptase serves as mRNA (Rosenthal, 2006; Rosenthal & Tan, 2011). The major virus families can be classified based on their genome, size, and whether they are enveloped or not enveloped (Rosenthal & Tan, 2011) (Fig. 1).

During the process of viral reproduction, a virus induces a living host cell to synthesize the essential components for the synthesis of new viral particles. The particles are then assembled into the correct structure, and the newly formed virions escape from the host cell to infect other cells. Therefore, the antiviral agents inhibit the virus infection by specifically targeting any step in viral reproduction. In general, the specific viral replication steps are: 1) attachment, 2) penetration, 3) uncoating, 4) replication, 5) maturation and assembly, and 6) release (Fig. 2). The first step in the virus replication process is attachment. In this case, the antiviral agents may act by blocking the fusion between the viral lipid envelope and host plasma membrane. The second step in viral replication cycle is penetration, thus the antiviral agents targeting this step inhibit fusion of the viral membrane with the cell membrane. In the following step, inhibitors of virus uncoating inhibit the virus proteases to avoid the complete release of virus genetic nucleoproteins. In the replication step, some antiviral agents can inhibit the action of polymerase, nucleoside reverse transcriptase (NRT), non-nucleosides reverse transcriptase (NNRT) or RNA polymerase. The maturation and assembly step is blocked by inhibiting the viral protein synthesis. All viruses use the cellular ribosomes to translate their viral mRNA. mRNA is translated into the structural proteins that will constitute core, envelope proteins and viral enzymes. In this step antiviral agent can specifically inhibit protease and integrase action. In the last step of viral replication, new virus particles are released from infected host cells. In general, lytic viruses are released by lysis and death of the host cell. Others exit by budding from the cell surface (Said & Abdelwahab, 2013).
In this sense, bioactive compounds from natural products still provide an important and diverse potential resource against pathogens. Particularly, fungi constitute a substantial source of bioactive molecules that could be used as potential antivirals agents. Fungi

growing in extraordinary environments such as endophytic and marine fungi contain and/or produce several molecules with antiviral activity that could be employed in other hosts (Linnakoski *et al*., 2018). In addition, culinary and medicinal mushrooms have several valuable impacts on human well-being. Fungal bioactive compounds can be divided in small organic molecules (secondary metabolites) produced by filamentous fungi and high molecular weight compounds obtained from the fruiting bodies of edible or medicinal mushrooms (Suwannarach *et al*., 2020). Fungal compounds with antiviral activities have been identified, which represents an important emerging field of study. In this review, we describe the fungal natural compounds that have shown antiviral activity against some human pathogenic viruses, such as human immunodeficiency virus, dengue virus, herpes simplex virus, bovine herpes virus, influenza virus, respiratory syndrome virus, hepatitis virus among others. We focused on the biosynthetic pathways of fungal bioactive compounds and addressed current knowledge about their antiviral mechanisms of action and specific targets.

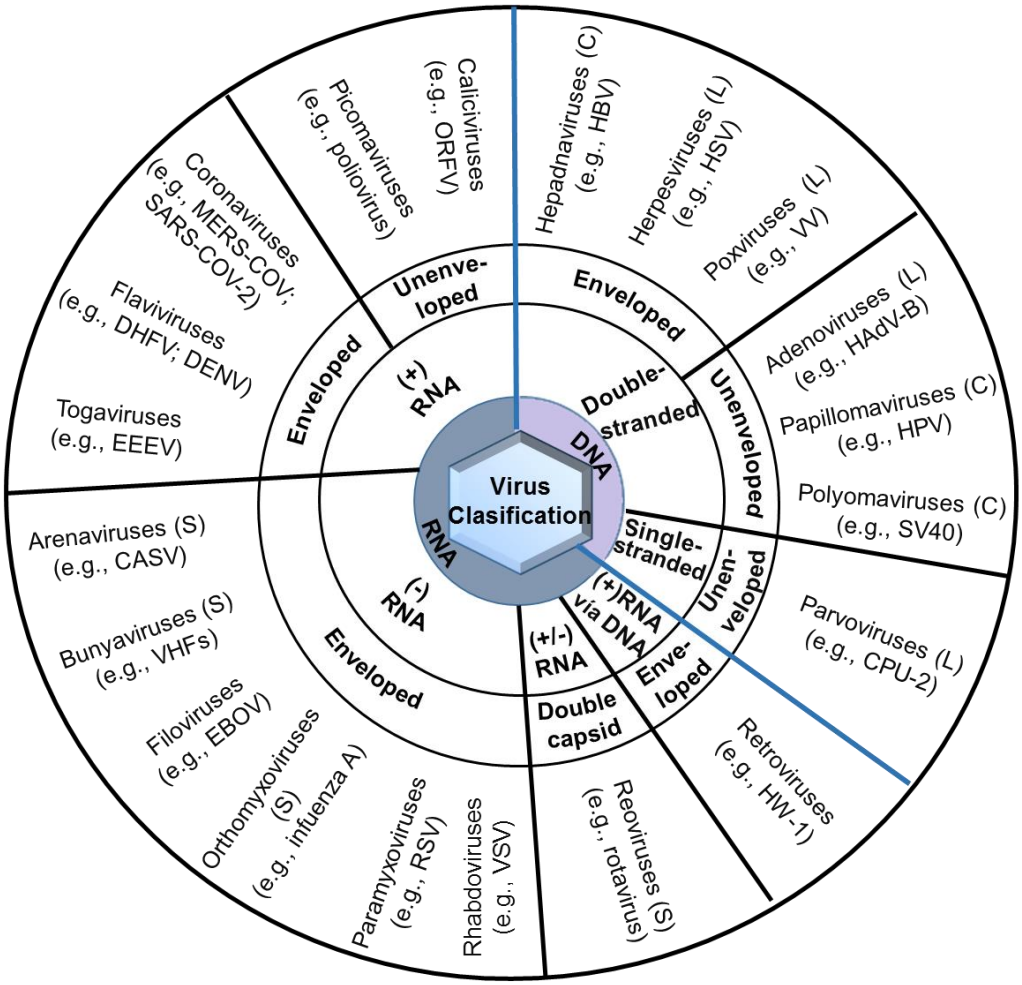

Fig. 1. Classification of major viral families based on genome structure and morphology, showing some virus examples. L, linear genome; C, circular genome; S, segmented genome.

MERS-CoV, Middle East Respiratory Syndrome Coronavirus; SARS-CoV (SARS-CoV-2, the virus responsible for the disease COVID-19), Severe Acute Respiratory Syndrome-Coronavirus; RSV, Respiratory Syncytial Virus; EBOV, Ebola Virus; HPV; Anogenital Human Papilloma Virus; HBV, Hepatitis B virus; DHFV, Dengue And Dengue Hemorrhagic Fever Virus; CASV; Corallus Annulatus Virus; ORFV, Oral Fecal Viruses; EEEV, Eastern Equine Encephalitis Virus; VHFs, Viral Hemorrhagic Fevers; VSV, Vesicular Stomatitis Virus; CPV-2; Canine Parvovirus-2; SV40, Simian Virus 40; HAdV-B, Respiratory Disease Human Adenovirus; VV, Varicela Virus; HIV-1, Human Immunodeficiency Virus; HSV, Herpes Simplex Virus.

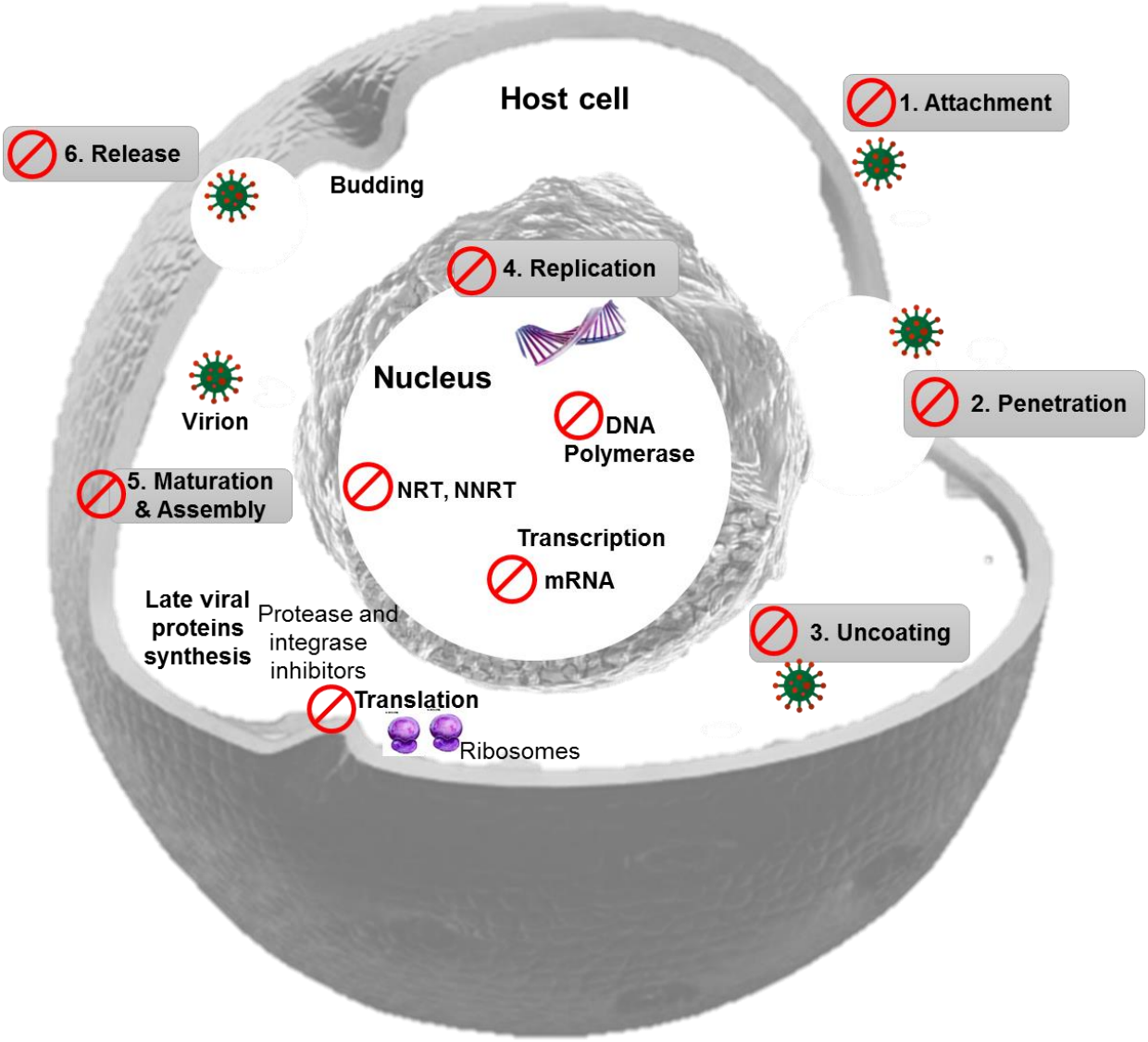

Fig. 2. Schematic representation of potential antiviral targeting steps in a virus replication cycle. In general, the specific viral replication steps are; 1) attachment, 2) penetration, 3) uncoating, 4) replication, 5) maturation and assembly and 6) release. NRT, nucleoside reverse transcriptase; NNRT, non-nucleosides reverse transcriptase.

2. FUNGAL GROWTH AND HYPHAL MAJOR COMPONENTS

Fungi comprise a large and diverse kingdom of eukaryotic organisms morphologically classified as yeasts, filamentous fungi, or dimorphic fungi (Moore *et al*., 2020; Sánchez *et al*., 2020). These organisms can be saprotrophs (decomposing dead material), obligated or opportunistic organisms (decomposers, mutualists or pathogens) (Schmit & Mueller, 2007). Fungi are found in different habitats and some of them have evolved to adapt and grow under extreme conditions (Raghukumar, 2017). In the fungal growth, after spore germination or inoculation of *in vitro*-grown mycelia, the substrate is invaded by microscopic filaments called hyphae. The cells in a hypha are separated by a septum, which is a cross-wall with a (usually central) pore. Hyphae continually grow and branch to form a network of hyphae or mycelia (mycelial growth), absorbing digestive products and penetrating the substrate to some extent. Mycelial growth occurs coupled simultaneously with increased enzyme production and respiration. Fungi release digestive enzymes by exocytosis from their hyphae, which break down substrates into smaller molecules for import into the hypha, releasing CO_2 and H_2O by respiration under aerobic conditions when mineralization of the substrate occurs (Pathak & Navneet, 2017).

Most cell walls are layered, and the innermost layer (that is, the layer immediately surrounding the plasma membrane) is a relatively conserved structural skeletal layer and the outer layers are more varied between species and are dynamically tailored to needs of the organism as it develops and matures and in response to interactions with the environment. Proteins rarely make up more than 20% of the wall material, and most are glycoproteins. Some proteins have a structural role, but most contribute to the many other functions. Proteins at, or close to, the outer surface determine the surface properties of the wall; that is, whether it is hydrophobic or hydrophilic (= non-wettable or wettable), or adhesive, or antigenic. The low concentrations of lipids and waxes found in fungal walls usually serve to control water movement, especially to prevent desiccation. Approximately 80% of the wall consists of polysaccharides. In hyphae a major component of the wall, and certainly the most important to structural integrity, is chitin, which is a β1,4-linked long polymer of N-acetylglucosamine. Walls of filamentous fungi, such as *Neurospora* and *Aspergillus*, contain 10–20% chitin, in almost all fungi, the main bulk component of the cell wall is a branched β1,3-glucan that is linked to chitin by a β1,4 linkage with interchain β1,6 glucosidic linkages. Chitin accounts for only 1–2% of the yeast cell wall by dry weight, the yeast wall being mainly composed of mannans, rather than glucans. However, in both situations the polysaccharides are frequently cross linked to other wall constituents, which often include complex polysaccharides, like gluco-galacto-mannans (Moore *et al*., 2020).

Fungi produce a very diverse range of secondary metabolites, which are structurally heterogeneous low-molecular-mass molecules that do not contribute to normal growth of the organisms that produce them. Secondary pathways become operational (or amplified) when growth rate is limited in some way to a level below the maximum. Secondary metabolism is a common feature of fungi. It consists of a relatively small number of enzymological processes (often of relatively low substrate specificity) which

convert a few important intermediates of primary metabolism into a wide range of products (Bu'Lock, 1967).

Microorganisms that produce these metabolites use them to defend their habitat, as symbiosis agents, as chemical signals for communication or to inhibit the growth of competitors (Brakhage, 2012). Secondary metabolites are very important for society since some of them have important pharmacological applications. In particular, mushrooms are a very large and diversified group of macrofungi belonging to basidiomycetes and ascomycetes, which have two phases of growth: the reproductive phase (fruit bodies) and the vegetative phase (mycelia). These organisms are epigeous, which means that they grow above the earth, with the umbrella-shaped fruiting body, where spores are produced on lamellae, structures on the underside of the pileus.

The fungal spores for these two groups are located in a special structure called 'ascus' (for ascomycetes) or on a 'basidium' (for basidiomycetes) (Sánchez, 2017). Mushrooms have been eaten and appreciated for their exquisite flavour and are important for their economic and ecological values, and medicinal properties.

Fruiting bodies of mushrooms from the *Agaricus*, *Pleurotus* and *Lentinula* genera are reported as the most cultivated and commercialized in the world (Sánchez, 2010). In general, mushrooms contain 10% dry matter and 90% water (Sánchez, 2010). These organisms contain vitamins (e.g. ascorbic acid, thiamine, riboflavin and niacin), ergosterol and essential amino acids. They also have proteins, essential fatty acids (e.g. linoleic, oleic, and linolenic acids), ash, and glycosides. Volatile oils, phenolic compounds, tocopherols, carotenoids, flavonoids, folates, organic acids, etc (Patel & Goyal, 2012; Sande *et al*., 2019). Therefore, some fungal compounds with antiviral activity can be produced as secondary metabolites and in other cases antiviral compounds can be present in the hyphae of fruit bodies of edible or medicinal mushrooms (Fig. 3).

3. FUNGAL BIOACTIVE COMPOUNDS WITH ANTIVIRAL EFFECT

Several studies have demonstrated antiviral capabilities of different fungal compounds mainly from ascomycetes and basidiomycetes (Table 1). Some of these compounds are small organic molecules produced by hyphae and then excreted, which are usually studied in extract of the culture medium. In particular, these bioactive molecules with antiviral effect have been classified as polyketides, indole alkaloids, terpenoids, non-ribosomal peptides, polyketides, and hybrids of non-ribosomal peptides, fatty acids, ergosterol peroxide etc. These fungal bioactive compounds have been reported to be produced by *Lignosus, Penicillium, Stachybotrys, Aspergillus, Cladosporium, Alternaria, Ganoderma, Fusarium, Phoma and Xylaria species among others* (He *et al*., 2013; Peng *et al*. 2013: Raekiansyah *et al*., 2017; Zhao *et al*., 2017; Sillapachaiyaporn & Chuchawankul, 2020) (Table 1).

On the other hand, the antiviral effect of fungal high molecular weight compounds, which are extracted from fungal mycelia and fruit bodies have been reported as polysaccharides (e.g., glucan, mannan and lentinan), polysaccharide-protein/amino acid

complexes and proteins from genera such as *Agaricus*, *Cordyceps*, *Ganoderma*, *Grifola*, *Inonotus* and *Pleurotus* (Jiang *et al*. 2011; Yamamoto *et al*., 2013; De Sousa-Cardozo *et al*., 2014; Bharadwaj *et al*., 2019).

Some of the virus target in which fungal antiviral compounds have been tested are; human immunodeficiency virus (HIV-1), dengue virus (DENV), herpes simplex virus (HSV), bovine herpes virus (BoHV), hepatitis C virus (HCV), hepatitis B virus (HBV), influenza virus, porcine reproductive and respiratory syndrome virus (PRRSV) and poliovirus. Table 1 shows that some mechanisms of action of fungal bioactive compounds against virus reproduction can be through inhibition of any of the following steps; penetration, replication or translation. These molecules can also inhibit either the viral integrase or viral protease action. For example, a sulfated β-D glucan from *Agaricus brasiliensis* was able to inhibit viral penetration, showing a half maximal inhibition concentration (IC_{50}) value of 8.39 µg mL^{-1} (De Souza-Cardozo *et al*., 2014). In addition, a protein and a ganoderic acid isolated from *Grifola frondosa* and *Ganoderma lucidum*, respectively, were found to be viral replication inhibitors showing IC_{50} values of 4.1 and 8 µg mL^{-1}, respectively (Li & Wang., 2006; Gu *et al*., 2007). Furthermore, an ubiquitin-like protein from *Pleurotus ostre*atus was reported to inhibit viral translation (Wang & Ng, 2000).

On the other hand, equisetin (which was first isolated from *Fusarium equiseti*), phomasetin and integric acid, bioactive compounds found in *Fusarium heterosporum*, *Phoma* sp and *Xylaria* sp, respectively, were able to inhibit the viral integrase showing an IC_{50} between 5 and 25 µM (Singh *et al*., 1998; Hazuda *et al*., 1999; Sims *et al*., 2005) (Table 1).

In addition, bioactive compounds isolated from fruit bodies of *Ganoderma*, *Auricularia* and *Cordyceps* genera were found to be protease inhibitors (El Dine *et al*., 2008; Sato *et al*., 2009; Jiang *et al*., 2011; Bharadwaj *et al*., 2019; Sillapachaiyaporn *et al*., 2019). In particular, the IC_{50} values for ganodermanotriol, ganoderic acid GS-2 and ganoderiol F, which are protease inhibitors from *Ganoderma* species range between 20 and 50 µM (Sato *et al*., 2009; Bharadwaj *et al*., 2019) (Table 1).

According to the findings of previous studies, drugs or compounds that act against virus by inhibiting proteases have been considered as potential drugs against coronavirus (CoVs) (Suwannarach *et al*., 2020). On the other hand, ribonucleases (RNases) also act as antiviral proteins as they inhibit the reproduction of viruses. All microorganisms contain different classes of RNases, which are hydrolytic enzymes that are involved in degradation of phosphodiester bond of cellular RNA. In particular, *Aspergillus* is one of the most prominent fungal genera in terms of both production and medical applications of fungal RNases (Kumar & Kanwar, 2017; 2018; 2020). However, RNases from *Rhizopus niveus*, *Ustilago sphaerogena* (Lacadena *et al*., 2007; Kumar & Kanwar, 2017, 2018), *Fusarium moniliforme* (Yoshida *et al*., 1980), *Penicillium brevicompactum* (Shlyapnikov *et al*., 1984) and *Penicillium chrysogenum* (Yakovlev *et al*., 1980) have also been studied.

Table 1. Antiviral active compounds from fungi, virus target, mechanism of action and half-maximal inhibition concentration (IC_{50})

Organism	Phyllum/ Edibility	Biomaterial source	Bioactive compound	Virus target	Mechanism of action	IC_{50}	Reference
Lignosus rhinocerus	Basidiomycota /E	Sclerotium extracts (crude hexane extract)	Fatty acids, peptides and terpenoids.	HIV-1	Inhibition of protease	0.53 mg/mL	Sillapachaiyaporn & Chuchawankul, 2020
Ganoderma lucidum	Basidiomycota /E	Purchased ganoderma notriol	Ganodermanotriol	DENV	Inhibition of protease	25-50 µM	Bharadwaj *et al*., 2019
Auricularia polytricha	Basidiomycota /E	Sun-dried fruit body	Triacylglycerols, linoleic acid and ergosterol.	HIV-1	Inhibition of protease	0.80 mg/mL	Sillapachaiyaporn *et al*., 2019
Penicillium sp.	Ascomycota/NE	Extracts from culture broth	Brefeldin A	DENV	Affect early stage of the virus reproduction	54.6-65.7 nM	Raekiansyah *et al*., 2017
Stachybotrys chartarum	Ascomycota/NE	Extracts from fermentation broth	Stachybotrysams A Stachybotrysams B Stachybotrysams C (farnesylated isoindolinone derivatives)	HIV	NR	9.3 µM 1.0 µM 9.6 µM	Zhao *et al*., 2017
Agaricus brasiliensis	Basidiomycota /E	Dried fruit body	Sulfated (1→6)-(1→3)- β-D-glucan	HSV-1 HSV-2	Inhibition of penetration	8.39 µg/mL 2.86 µg/mL	De Sousa-Cardozo *et al*., 2014
Agaricus	Basidiomycota	Dried fruit	Polysaccharide	HSV-1	NR	454	Yamamoto *et al*.,

brasiliensis	/E	body				µg/mL	2013
			Polysaccharide sulfated derivative	HSV-1	NR	346 µg/mL	
Agaricus brasiliensis	Basidiomycota /E	Dried fruit body	Polysaccharide	BoHV-1	NR	634 µg/mL	Yamamoto *et al*., 2013
			Polysaccharide sulfated derivative			830 µg/mL	
Aspergillus terreus	Ascomycota/NE	Extracts from fermentation broth	cyclic tetrapeptide (asperterrestide A)	Influenza (H1N1)	NR	15 µM	He *et al*., 2013
				Influenza (H3N2).	NR	8.1 µM	
Cladosporium sp.	Ascomycota/NE	Extracts from fermentation broth	A glyantrypine derivative and a pyrazinoquinazoline derivative and three alkaloids		NR	82–89 µM	Peng *et al*., 2013
Aspergillus nidulans (=Emericella nidulans)	Ascomycota/NE	Extracts from fermentation broth	Ethyl acetate extract Sterigmatocystin Emericellin Cordycepin Ergosterol peroxide Myristic acid	HCV	Inhibition of protease	30 48.5 50 24.5 47 51 (µg/mL)	Hawas *et al*., 2012
Alternaria sp	Ascomycota/NE	Extracts from fermentation broth	Alterporriol Q	PRRSV	NR	39 µ	Zheng *et al*., 2012
			Tetrahydroaltersolanol C	PRRSV	NR	65 µM	
NR	Ascomycota/NE	Extracts from fermentation broth	(3R,11R), (4E,8E)-3-hydroxy-11-methyloxacyclododeca-4,8-diene-1,7dione	HSV-1	NR	0.45 µM	Shushni *et al*., 2011
Penicillium	Ascomycota/N	Extracts	Purpurquinone B	Influenza	NR	61.3 µM	Wang *et al*., 2011

purpurogenum	E	from fermentation broth	Purpurquinone C Purpurester A, TAN-931	(H1N1)		64.0 µM 85.3 µM 58.6 µM	
Emericella sp.	Ascomycota/NE	Extracts from fermentation broth	4-hydroxy-5,6-dimethoxy-2,3dihydro-1H-isoindol-1-one.	Influenza A (H1N1)	NR	42.07 µg/mL	Zhang *et al*., 2011
			Emerimidine B	Influenza A (H1N1)	NR	62.05 µg/mL	
Cordyceps militaris	Ascomycota/E	Dried fruit body	Adenosine, 6,7,2',4',5'-pentamethoxyflavone, dimethylguanosine	HIV-1	Inhibition of protease	NR	Jiang *et al*., 2011
Ganoderma sinense	Basidiomycota/E or NE	Dried fruit body	Ganoderic acid GS-2, 20-hydroxylucidenic acid N, 20(21)-dehydrolucidenic acid N, ganoderiol F	HIV-1	Inhibition of protease	20-40 µM	Sato *et al*., 2009
Ganoderma colossum	Basidiomycota/NE	Dried fruit body	Lanostane triterpenes	HIV-1	Inhibition of protease	5-13 µg/mL	El Dine *et al*., 2008
Agaricus brasiliensis (previously named Agaricus blazei ss. Heinem),	Basidiomycota/E	Dried fruit body	Aqueous extract Ethanol extract Isolated polysaccharide	Poliovirus type 1	NR	922 187 92 (µg/mL)	Faccin *et al*., 2007
Grifola frondosa	Basidiomycota/E	Dried fruit body	Protein	HSV-1	Inhibition of replication	4.1 µg/mL	Gu *et al.,* 2007
Ganoderma lucidum	Basidiomycota/E	Extracts from fermentation broth	Ganoderic acid	HBV	Inhibition of replication	8 µg/mL	Li *et al*., 2006
Ganoderma	Basidiomycota	Air-dried	Ganoderone A,	HSV	NR	0.3	Niedermeyer *et*

pfeifferi	/NE	fruit body	lucialdehyde B ergosta-7,22-dien-3β-ol	HSV HSV	NR NR	0.075 0.03 (µg/mL)	*al*., 2005
Ganoderma pfeifferi	Basidiomycota /NE	Dried fruit body	Ganodermadiol	HSV-1	NR	0.068 mmol/L	Mothana *et al*., 2003
			Lucidadiol	Influenza virus type A	NR	0.22 mmol/L	
			Applanoxidic acid	Influenza virus type A	NR	0.22 mmol/L	
				Influenza virus type A	NR	0.19 mmol/L	
Inonotus hispidus	Basidiomycota /NE	Dried fruit body	Hispolon and hispidin (phenolic compounds)	Influenza viruses type A and B	NR	NR	Awadh *et al*., 2003
Ganoderma lucidum	Basidiomycota /E	Fruit body	Acidic protein bound polysaccharide	HSV-1 HSV-2	NR	300 440 (µg/mL)	Kim *et al*., 2000
Pleurotus ostreatus	Basidiomycota /E	Fruit body	Ubiquitin-like protein	HIV	Inhibition of translation	160 nM	Wang & Ng, 2000
Fusarium heterosporum	Ascomycota/NE	Extracts from fermentation broth	Acyl tetrameric acid (equisetin)	HIV-1	Inhibition of integrase	15-25 µM	Hazuda *et al*., 1999; Sims *et al*., 2005
Phoma sp	Ascomycota/NE	Extracts from fermentation broth	Acyl tetrameric acid (phomasetin)	HIV-1	Inhibition of integrase	18 µM	Hazuda *et al*., 1999

Xylaria sp,	Ascomycota/NE	Extracts from fermentation broth	Acyl eremophilane sesquiterpenoid (integric acid)	HIV-1	Inhibition of integrase	5-10 µM	Hazuda *et al*., 1999

HIV-1, Human Immunodeficiency Virus; DENV (Dengue Virus); HSV, Herpes Simplex Virus; BoHV, Bovine Herpes Virus; HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; PRRSV, Porcine Reproductive and Respiratory Syndrome Virus
E, Edible.
NE, Not edible.
NR; Not reported

4. BIOSYNTHETIC PATHWAYS OF FUNGAL BIOACTIVE COMPOUNDS WITH ANTIVIRAL ACTIVITY

Ergosterol from *Auricularia polytricha* and triterpenes (e.g., ganoderic acids) from *Ganoderma* genera have been reported as antiviral compounds. Ergosterol is present in the fungal membrane and ganoderic acids are secondary metabolites produced by *Ganoderma* species (Fig. 3). In particular, more than 150 ganoderic acids have been identified, and the genome of *Ganoderma lucidum* has been sequenced for the study of specialized metabolic pathways (Kues *et al*., 2015; Yang *et al*., 2018). Biosynthesis of ergosterol and ganoderic acids as well as other types of triterpenes is considered to begin from acetyl-coenzyme A and progress via the mevalonate pathway, as mevalonate is considered to be the precursor (Fig. 4). The mevalonate pathway has been shown to be active in *G. lucidum* and can be described in four main processes (Shi *et al*., 2010). These processes are catalyzed by several enzymes, which are shown in Fig. 4. In the first process the acetyl-CoA is converted to isopentenyl pyrophosphate (isopentenyl PP). Subsequently, geranyl pyrophosphate, farnesyl diphosphate, and geranylgeranyl pyrophosphate are formed through the action of various prenyltransferases from their isopentenyl PP precursor.

In the third process, these intermediates can self-condense and are used in alkylation reactions to generate prenyl side chains for several of nonterpenoids or form a ring to make the basic parent structures of the sundry terpenoid families. In the last process, oxidation, reduction, isomerization, conjugation, or other secondary transformations form ganoderic acids (and different types of triterpenes), ergosterol and zymosterol. (Shi *et al*., 2010). Recently, the genes (CYP512U6 and GLCPR), which are involved in the biosynthesis of ganoderic acids in *G. lucidum* have been characterized and cloned (Yang *et al*., 2018).

Ergosterol peroxide is another fungal derived compound, which has been found to have antiviral effects (Hawas *et al*., 2012) (Table 1). Ergosterol peroxide is a lipid-soluble steroid derivative mainly found in fungal biomass (mycelium and fruit bodies (Merdivan & Lindequist, 2017; Fijałkowska *et al*., 2020). It has often been detected in medicinal mushrooms and is considered an important metabolite, however, it still not clear whether ergosterol peroxide is natural to biological sources or an artefact formed from ergosterol during the isolation process (Merdivan & Lindequist, 2017). A proposed pathway for ergosterol peroxide biosynthesis is shown in Fig. 5. The ergosterol peroxide can be formed via the mevalonate pathway. Firstly, squalene is formed from two molecules of farnesyl pyrophosphate, which is the precursor of all steroids and then squalene is converted into lanosterol by the action of an epoxidase and a synthase. Lanosterol is then transformed to zymosterol through a series of demethylation, reduction and desaturation reactions catalyzed by diverse enzymes. Zymosterol is converted into fecosterol, followed by the formation of episterol, which is desaturated and reduced to ergosterol (Klug & Daum, 2014). Finally, ergosterol would be transformed into ergosterol peroxide after UV irradiation in the presence of O_2 (Fig. 5). All those genes involved in the biosynthesis of ergosterol are already known (Jordá, & Puig, 2020).

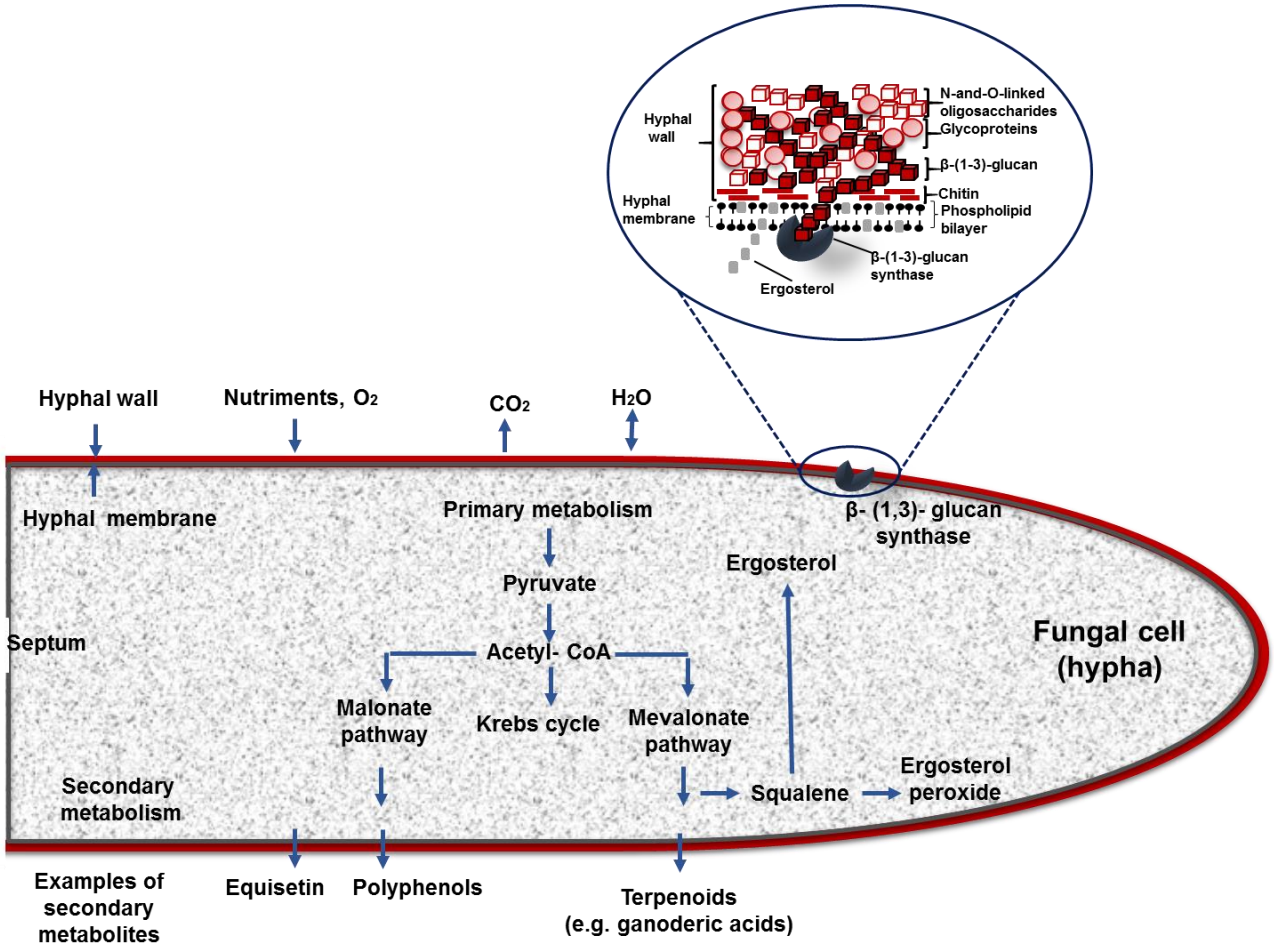

Fig. 3. Overview on the major pathways for synthesis of antiviral active compounds produced as secondary metabolites in hypha and fungal cell wall composition.

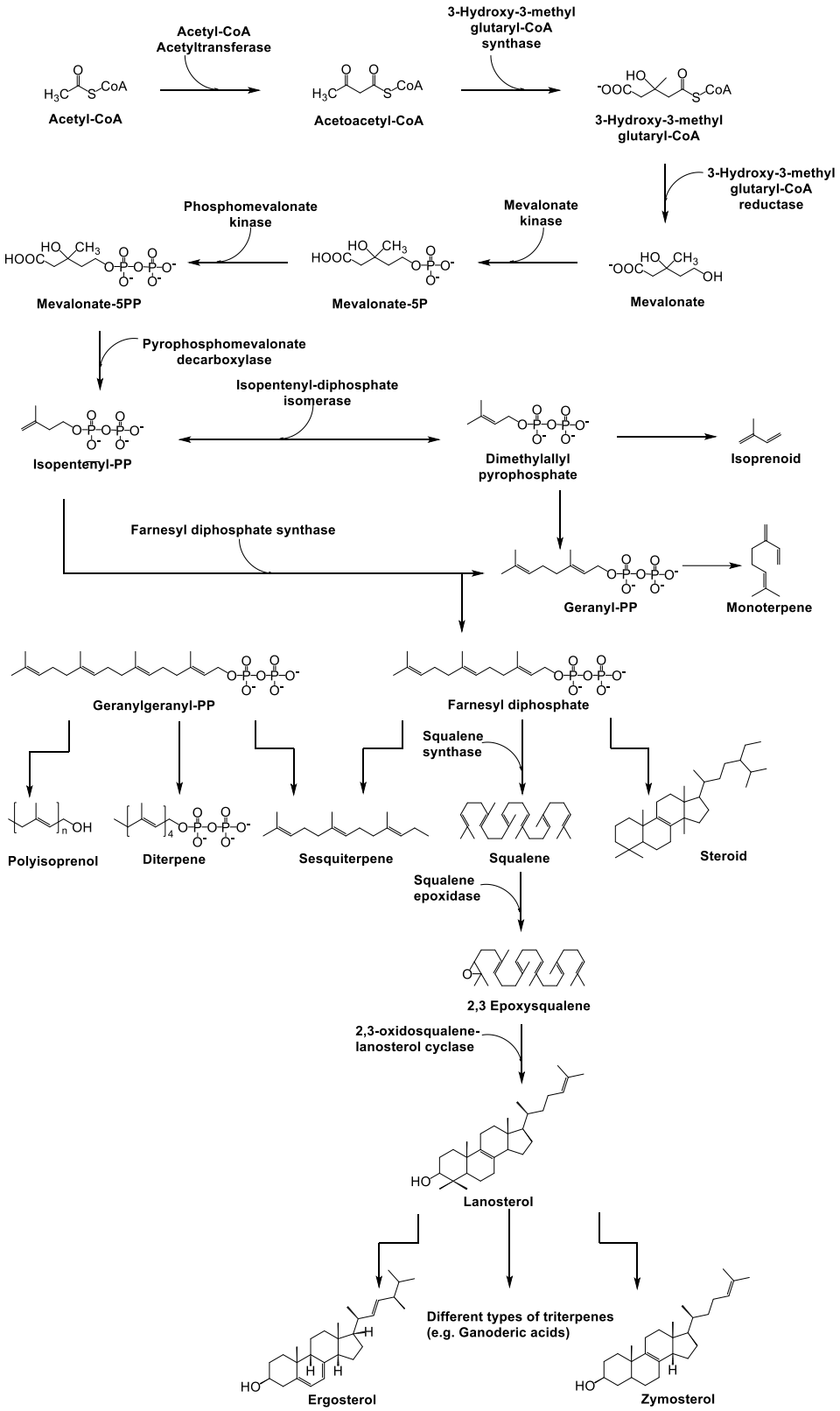

Fig. 4. Biosynthetic pathway of ganoderic acids and ergosterol, fungal bioactive compounds with antiviral activity. Redrawn from Shi *et al*., 2010.

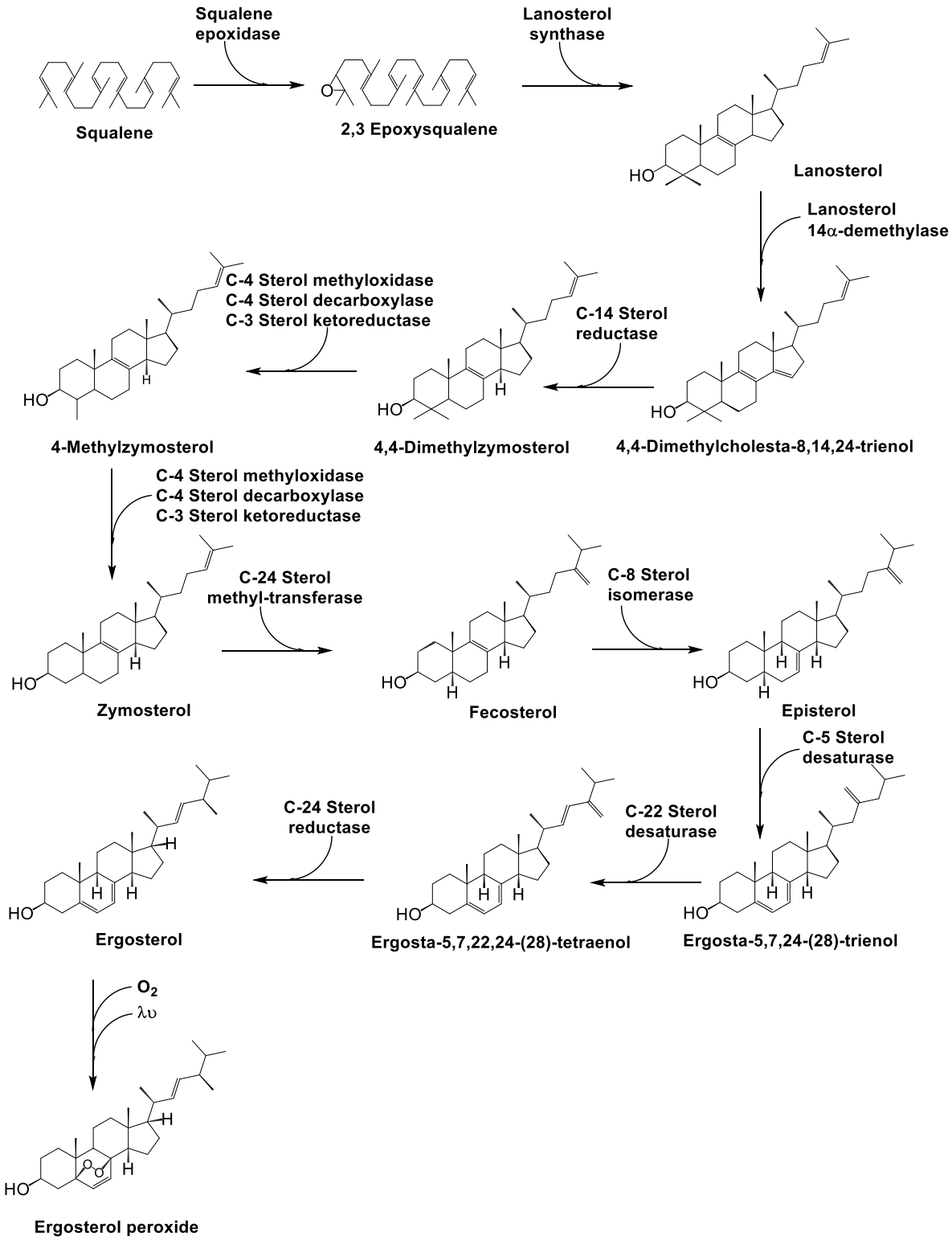

Fig. 5. Proposed biosynthetic pathway of ergosterol peroxide, fungal bioactive compound with antiviral activity. Ergosterol pathway was redrawn from Klug & Daum, 2014

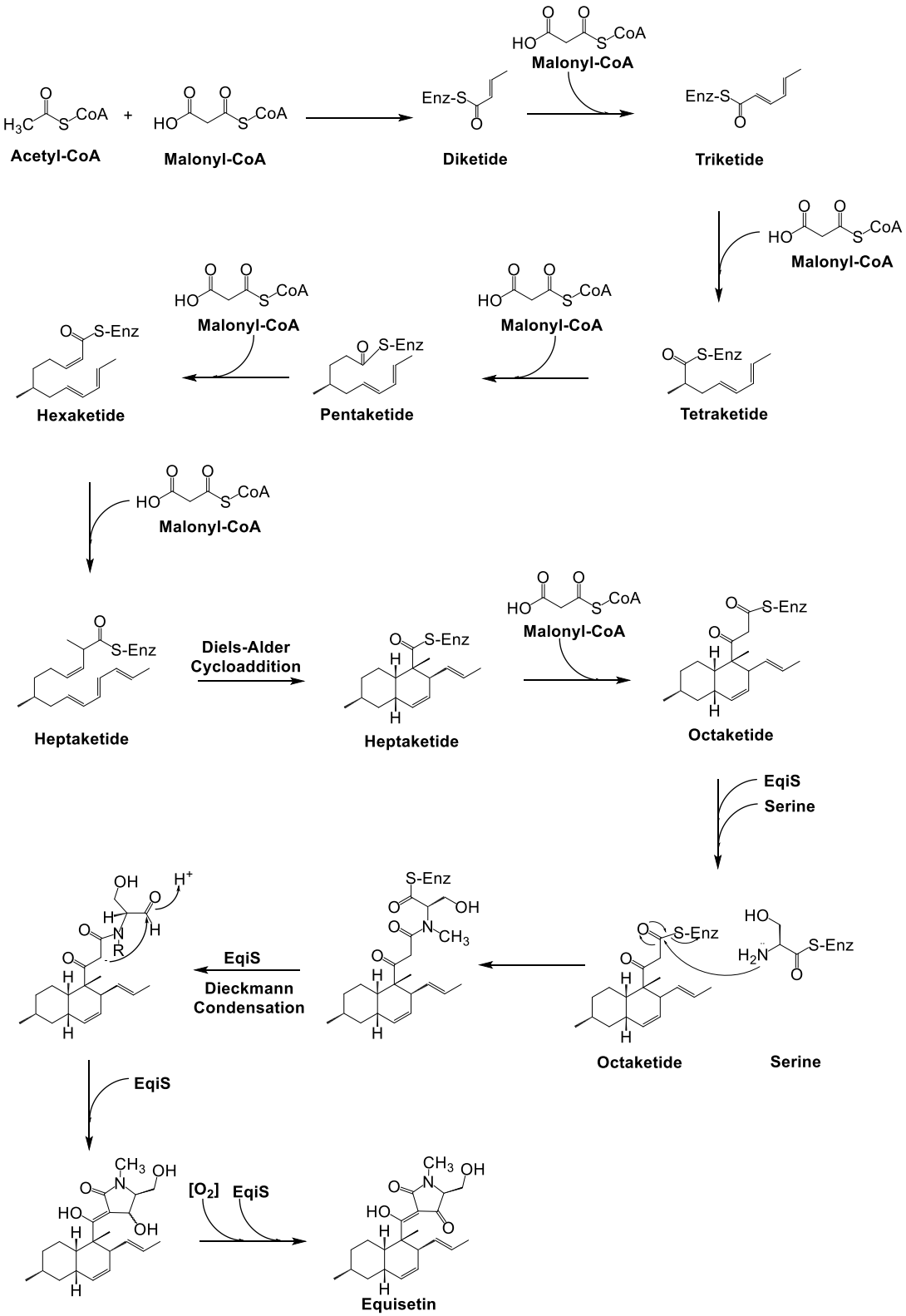

Fig. 6. Biosynthetic pathway of equisetin, a fungal bioactive compound from *F. heterosporum* with antiviral activity. EqiS; polyketide synthase, previously described (Campbell & Vederas, 2010; Sims *et al*., 2005). Redrawn from Sims *et al*., 2005.

5. CONCLUSION AND PERSPECTIVES

Bioactive compounds isolated from fungi (both edible and nonedible) have shown potential activity against viruses such as human immunodeficiency virus, dengue virus, herpes simplex virus, bovine herpes virus, hepatitis C virus, hepatitis B virus, influenza virus, porcine reproductive and respiratory syndrome virus, and poliovirus among others. These compounds are able to inhibit viral reproduction, blocking viral penetration, replication or translation as well as the integrase or protease action. Previously, studies have shown that viral protease inhibitors are effective against coronavirus. Therefore, fungal compounds able to inhibit protease (e.g. ganodermatriol, ergosterol, terpenoids, ganoderic acid GS-2, ganoderiol, sterigmatocystin, emericellin, cordycepin, ergosterol peroxide, myristic acid among others), may have a significant value to society at present, as they may have the potential to treat severe viral respiratory infections. However, extensive investigations on clinical trials are required for the introduction of new antiviral agents into the market.

Further research supported by advances in understanding molecular mechanisms ~~of~~ by which fungal bioactive compounds exhibit antiviral activity, the regulation mechanisms of their biosynthetic pathways and the use of new biotechnological tools to improve production will reveal the most cost-effective production processes.

In addition, extensive studies are required to detect more potential fungal bioactive compounds with antiviral effect, such as ribonucleases and deoxyribonucleases (RNases and DNases) to inhibit the reproduction of viruses.

Fungi represent a potential natural source of bioactive molecules that can be exploited for treating viral infections, which represent one of the main causes of human disease worldwide.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare

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