Edible mushrooms of the genus *Pleurotus* as biocontrol agents of parasites of importance for livestock

Los hongos del género *Pleurotus* como agentes de biocontrol de parásitos de importancia pecuaria

Tania María Rodríguez-Barrera[1, 2], Maura Téllez-Téllez[2], José E. Sánchez[3], Gloria Sarahí Castañeda-Ramirez[1], Ma. de Lourdes Acosta-Urdapilleta[2], Carlos Ramón Bautista-Garfias[1], Liliana Aguilar-Marcelino[1]

[1] Centro Nacional de Investigación Disciplinaria en Salud Animal e Inocuidad, INIFAP, km 11 carretera federal Cuernavaca-Cuautla, No. 8534, Col. Progreso, C.P. 62550, Jiutepec, Morelos, México.
[2] Centro de Investigaciones Biológicas de la Universidad Autónoma del Estado de Morelos Av. Universidad No. 1001, Col. Chamilpa Cuernavaca, C.P. 62209, Morelos, México.
[3] El Colegio de la Frontera Sur, km 2.5 carretera al Antiguo Aeropuerto, C.P. 30700, Tapachula, Chiapas, México.

RESUMEN

Antecedentes: Los hongos comestibles presentan propiedades nutracéuticas principalmente para los humanos, animales y plantas. Las especies de *Pleurotus* representan una alternativa de control de parásitos ya que tienen actividad nematicida contra diferentes géneros taxonómicos de nematodos de importancia pecuaria.

Objetivo: Presentar un panorama general sobre los hongos del género *Pleurotus* y sus características como método sustentable de biocontrol de nematodos parásitos de animales de importancia en salud pública.

Métodos: La revisión bibliográfica se llevó a cabo consultando estudios publicados sobre el género del hongo *Pleurotus* y sus propiedades, analizando lo referente a la actividad nematicida. Los trabajos fueron agrupados de acuerdo con su enfoque de investigación de trabajos en revistas indexadas y en la plataforma (Google academico), digital relacionada con palabras clave y temas del área pecuaria.

Resultados y conclusiones: *Pleurotus* spp. cuenta con diferentes metabolitos secundarios con actividad antiparasitaria principalmente antihelmíntica y particularmente contra nematodos gastrointestinales. Las características que tiene este hongo son excelentes para sus aplicaciones biotecnológicas ya que presenta una amplia gama de metabolitos secundarios en diferentes partes como son los basidiomas, el micelio y el sustrato degradado. Existen nuevas líneas de investigación que se deberán atender para demostrar su eficacia en biocontrol en el área pecuaria.

Palabras clave: hongos comestibles, antagonistas naturales, nematodos gastrointestinales, ganadería sustentable

ABSTRACT

Background: Edible mushrooms have nutraceutical properties, mainly in humans, animals and plants. *Pleurotus* species represent an alternative approach to parasite control because they have nematicidal activity against different taxonomic genera of nematodes of importance for livestock.

Objective: To present a general overview of fungi of the genus *Pleurotus* and their characteristics as a sustainable method of biocontrol for parasitic nematodes of animals with importance in public health.

Methods: This bibliographic review was carried out by consulting published studies on edible fungi of the genus *Pleurotus* and analyzing their properties related to nematicidal activity. The works were grouped according to their research focus; works related to keywords and topics in livestock were identified in indexed journals and on digital platforms (academic Google).

Results and conclusions: *Pleurotus* spp. produce different secondary metabolites with antiparasitic activities, mainly anthelmintic and particularly against gastrointestinal nematodes and their larval stages. The characteristics of these fungi are excellent for biotechnological applications since they produce a wide range of secondary metabolites in different parts, such as in the basidiomata, mycelia and degraded substrates. There are new lines of research that must be addressed to demonstrate their effectiveness in the area of biocontrol in livestock.

Keywords: Edible mushrooms, natural antagonist, gastrointestinal nematodes, sustainable livestock

CORRESPONDING AUTHOR
✉ Liliana Aguilar Marcelino, aguilar.liliana@inifap.gob.mx
ORCID: 0000-0002-8944-5430
José E. Sánchez, esanchez@ecosur.mx
ORCID: 0000-0003-0535-4302

INTRODUCTION

Livestock farming is one of Mexico's most important economic activities, and the country is ranked seventh in the world as a powerhouse in the generation of livestock products (FAO 2020). Livestock is a cost-effective sector that guarantees the production and supply of accessible, safe and quality food (Figueroa-Antonio *et al*. 2018). The livestock sector is affected by different diseases caused by parasites, such as gastrointestinal nematodes (GIN), which represent one of the most important health problems in livestock worldwide (Pinilla *et al*. 2018). Subclinical infections and the presence of GIN are determined by biotic and abiotic factors, such as climate, animal management and the age of hosts exposed to contaminated pastures (Byron *et al*. 2018). Parasitism caused by GIN causes economic losses in Mexico estimated at 35 billion pesos per year (FAO 2020). The economic losses are mainly caused by a decrease in milk and meat production and an increase in the costs associated with treatment and control of GIN (Pinilla *et al*. 2018).

Given this problem, it is essential to carry out studies to identify sustainable alternatives to control highly prevalent gastrointestinal parasites, as well as to understand their epidemiology and susceptibility to anthelmintic drugs (Byron *et al*. 2018).

Chemical products (e.g., macrocyclic lactones) used in an inadequate and constant manner can cause anthelmintic resistance (Lumaret *et al*. 2012, *Márquez*-Lara 2013). Additionally, the use of these chemical products threatens the environment (Martínez and Cruz 2009). Medicines, such as fenbendazole and oxfendazole, are excreted by ruminants in large quantities and put beneficial organisms, such as dung beetles (*Onthophagus landolti* and *Aphodius rufipes*), earthworms and nematophagous mites (*Caloglyphus mycophagus*), at risk (Aguilar-Marcelino *et al*. 2016, Quintero 2018).

Biocontrol can serve as an alternative to chemical products (Al-ani *et al*. 2020). Fungi are antagonists of parasitic nematodes of vertebrate animals, plants, insects and other pathogenic fungi (Fernández-Jiménez *et al*. 2019). They are excellent biocontrol agents due to their high reproductive capacity, specificity, production of resistant spores or development of saprophytic phases in the absence of their hosts, and antagonistic activities (Fernández-Jiménez *et al*. 2019). Barron and Thorn (1987) reported the mechanism of attack of *P. ostreatus* against the free-living nemato-

de *Rhabditis* spp. Initially, the mycelium of the fungus produces toxocysts, which are mainly composed of a nematotoxin called ostreanin, to attract the nematodes. Once the nematodes have made contact with the ostreanin, they become immobilized and the mycelium quickly penetrates their body through the oral cavity, anus and intercuticular spaces, allowing the fungus to subsequently feed on the nematode. The species of *Pleurotus* that showed this nematicidal activity are *P. strigosus*, *P. subareolatus* and *P. cornucopiae*. In addition, Li and Zhang (2014) reported 23 species of the genus *Pleurotus* with nematicidal activity. Based on the information that has been described to date, the objective of the present review was to analyze the characteristics of the genus *Pleurotus* as a biocontrol agent of parasites of importance for livestock.

PARASITES OF IMPORTANCE TO LIVESTOCK

A parasite is an organism that lives in another organism from which it feeds (SENASA 2017, Gutiérrez *et al*. 2020). Animals can become infected with parasites and can spread the infection. The animal on which the parasite feeds is called the host. The main helminths include the hematophagous nematode (*Haemonchus contortus*), cestodes (*Taenia saginata*) and trematodes (*Fasciola hepatica*) (SENASA 2017, Gutiérrez *et al*. 2020).

The GIN are found within the organs of the digestive tract, where copulation takes place between males and females, which produces eggs that are disposed of into the environment along with the animal's feces (Sutherland and Scott 2010). There are also other parasites that cause intestinal trichostrongylosis. The most important genera from a veterinary point of view are *Trichostrongylus*, *Cooperia* and *Nematodirus* (Von son-De-Fernex *et al*. 2016, Pinilla *et al*. 2018).

Gastroenteric parasitosis in ruminants mainly bovines and sheep are very important due to their cosmopolitan nature, causing great economic losses that can be direct such as the death of young animals or indirect that are clinically manifested by persistent diarrhea, anemia and malnutrition, resulting in stunted growth in young animals, as well as low production of meat and milk in adult animals (Valcárcel-Sancho *et al*. 2009, Liébano *et al*. 2011). In table 1, the most important gastrointestinal parasites (nematodes) of ruminants are presented.

Table 1. Gastrointestinal parasites (nematodes) of ruminants

Species	Organ
Haemonchus contortus	Abomasum
H. placei	Abomasum
Mecistocirrus digitatus	Abomasum
Trichostrongylus axei	Abomasum
T. colubriformis	Abomasum
T. longispicularis	Abomasum
Teladorsagia/Ostertagia circumcincta	Abomasum
O. trifurcata	Abomasum
O. lyrata	Abomasum
Nematodirus spathiger	Small intestine
N. fillicolis	Small intestine
N. helvetianus	Small intestine
N. battus	Small intestine
Strongyloides papillosus	Small intestine
Bunostomum trigonocephalum	Small intestine
B. phlebotomum	Small intestine
Cooperia oncophora	Small intestine
C. pectinata	Small intestine
Trichostrongylus spp.	Small intestine
Toxocara vitulorum	Small intestine

In rural areas of the country, animal husbandry is the main activity that supports the economy of producers and their families (López-González *et al.* 2012). However, this activity is carried out under precarious conditions that make the animals vulnerable to endemic diseases such as parasites; this has caused economic losses estimated at 35 billion pesos due to reductions in animal performance, deterioration of product quality and increased costs of prevention, control, treatment and animal death (FAO 2020). Parasitic diseases affect livestock production, as well as public health, and their risks are associated with production systems (SENASA 2017).

Parasites are very diverse and may vary from one region to another; however, the genera commonly found in Mexico are *Haemonchus*, *Trichostrongylus*, *Cooperia*, *Strongyloides*, *Nematodirus*, and *Oesophagostomum* (Rodríguez-Vivas *et al.* 2017).

Helminths are found in different climates thanks to their high reproductive capacity and various adaptation mechanisms in response to adverse environmental conditions. Parasite species in cattle prefer certain organs (Paredez-Martinez 2014). These parasites have a direct life cycle, with a free-living phase in the pasture and a parasitic phase in the animal. Most of these parasites infect animals via the oral route following ingestion of infectious larvae (L_3) present in water and food. Some factors favor the development of the parasites in the free-living phase, including humidity above 80 % and temperatures between 25-27 °C, which facilitate the evolution of the larvae over 7-10 days. Eggs are excreted with sheep feces into the grass, there they hatch into the larval stage and some migrate to pastures in water films, while others remain on the damp surface of the ground and manage to survive for months. In the dry season, larvae prefer wet sites because drying is detrimental to their survival (Paredez-Martinez 2014).

Haemonchus contortus
Haemonchus contortus is a nematode with blood-sucking habits, and it has 16 intestinal cells and a protective sheath in its infective stage (L_3) (Zajac and Garza 2020). While *H. contortus* is more prevalent in tropical climates, it is also present in various parts of the world and has a negative impact on the livestock sector (Widiarso *et al.* 2018).

Life cycle of *Haemonchus contortus*
The life cycle of the sheep parasitic nematode *H. contortus* is divided into two phases: 1) exogenous and 2) endogenous. The exogenous phase begins when the sheep expel the eggs into the pasture in their feces; under optimal conditions, the L_1 larvae develop. This occurs in 1-2 days, after which the eggs hatch and the free-living larvae (L_2) emerge. After seven days, they reach their infective stage, known as L_3. These larvae migrate to the upper parts of the pastures to be ingested by the animals along with the grass (Zajac and Garza 2020). The endogenous phase starts when the infectious larvae (L_3) have been ingested by the sheep, at which time it enters the digestive tract and develops into L_4 and later, into L_5. In this last stage the nematode is considered an adult (Sutherland and Scott 2010). It should be mentioned that stages L_4 and L_5 feed on blood and tissue, and this activity irritates the mucosa causing inflammation. In addition, as the nematodes extract considerable amounts of blood, anemia develops, which is manifested as paleness of the conjunctiva and gums. At this stage, the animals become indifferent and suffer from low food conver-

sion, their hair becomes brittle and dull, and the animals lose their appetite, rendering them unable to regain their normal weight, sometimes resulting in death (Gasque 2008) (Figure 1).

Pest control in the livestock arena

These parasites have traditionally been treated with regular administration of chemical drugs (anthelmintics) as a simple and "effective" way to alleviate parasitic diseases. However, many animals have high parasite loads and clinical features of parasitosis (Lobayan *et al*. 2017), as the parasites have developed resistance to the anthelmintic products administered (González-Garduño *et al*. 2003, Torres-Acosta *et al*. 2003, Lanusse *et al*. 2018).

Anthelmintic products are currently the main method used to control ruminant nematodes worldwide. They have different mechanisms of action, and avermectins, benzimidazoles and nicotinic agonists are the most common anthelmintics used in ruminants (Márquez-Lara 2013).

Ivermectins are one of the anthelmintics available and they are frequently used by producers. However, they have negative effects on the environment, especially on microfauna such as beneficial arthropod populations associated with feces (they mainly affect their larval forms) (Márquez-Lara 2013).

Anthelmintic resistance can be either intrinsic or acquired; in the former, a parasite is naturally resistant to an anthelmintic due to the absence of receptors or the inability of the product to enter the site of action, as occurs in the resistance of trematodes and cestodes to macrocyclic lactones. Acquired resistance occurs in parasites that were originally susceptible to the drug, but after genetic modifications of the parasite that become hereditary, they are no longer susceptible (Márquez-Lara 2013, Olazarán-Jenkins *et al*. 2019).

Sustainable alternatives: edible mushrooms

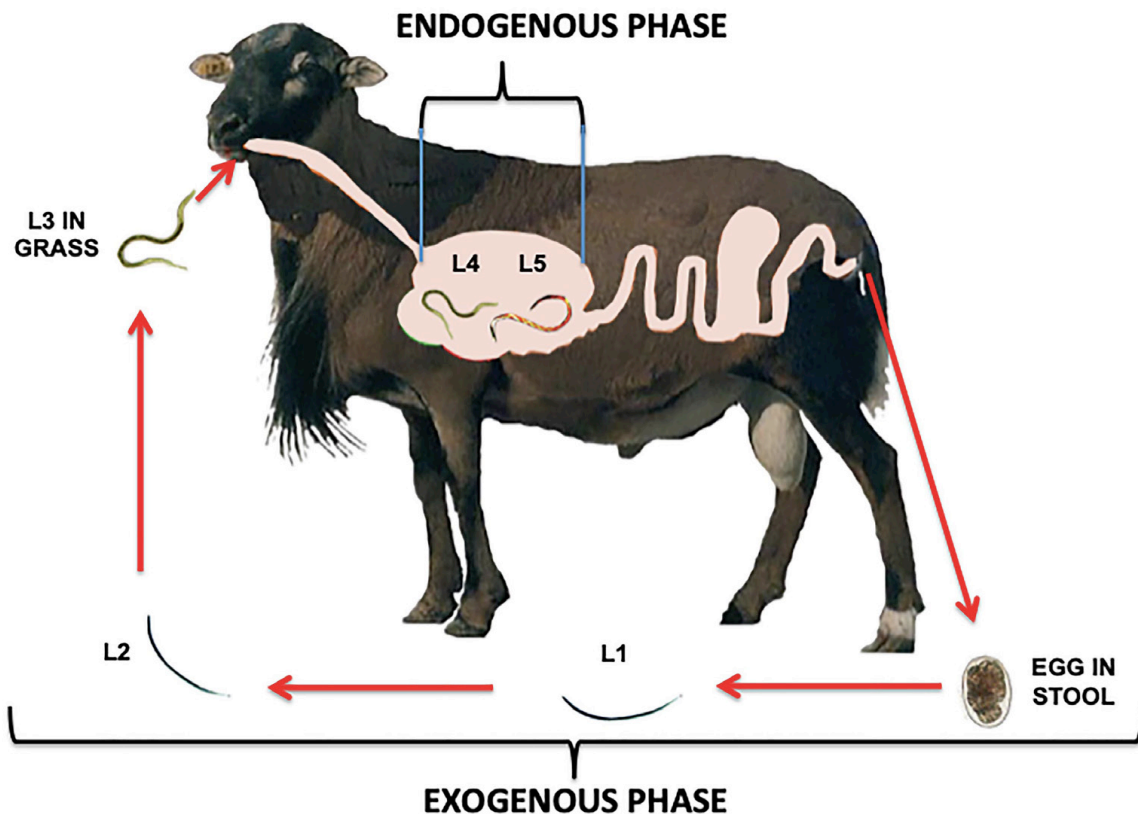An alternative method for parasite control in the livestock arena is edible mushrooms. Ascomycete, ba-

Figure 1. The biological cycle of nematode *Haemonchus contortus.* The exogenous phase showing the develop from eggs to the infectious larvae (L$_3$) and the endogenous phase showing the develop of the L$_3$ to L$_5$.

sidiomycete and zygomycete fungi have developed various strategies to attack nematodes, which are the most abundant organisms in the soil. They have developed these mechanisms to obtain the nitrogen requirements (van den Hoogen *et al.* 2019). In fact, Hyde *et al.* (2014) was the first to report a fungus with the capacity to trap nematodes corresponding to the species *Palaeoanellus dimorphus*, which lived 100 million years ago and are probably extinct today. Currently, fungi with nematicidal activity are distributed throughout the world. According to Li and Zhang (2014), there are 280 species belonging to 150 genera between the ascomycetes and basidiomycetes that have nematicidal capacity.

Barron and Dierkesy (1977) established that some species of *Hohenbuehelia*, and its anamorph *Nematoctonus*, had anthelmintic capacity. Furthermore, Barron and Thorn (1987) reported that the genus *Pleurotus* was more versatile than *Hohenbuehelia* because in addition to nematodes, other organisms could also serve as nutrients.

On the other hand, there are also nematodes that parasitize edible mushrooms and cause serious problems in their development and productivity. The most documented case is *Agaricus bisporus*, although the genus *Pleurotus* is not exempt from their attack (Belletini *et al.* 2018, Singh and Sharma 2016). Finally, there is also the case of beneficial nematodes for edible mushrooms that, being antagonists of their pests, are useful in biological control strategies (Choo *et al.* 2001, Rinker *et al.* 1995).

CLASSIFICATION OF NEMATOPHAGOUS FUNGI

Fungi are organisms that possess the ability to attack, kill and digest the body of nematodes (Rodríguez-Martínez *et al.* 2018). It has been observed that the mycelium of edible fungi can infect nematode eggs (Nordbring-Hertz *et al.* 2006). In addition to their nematicidal ability, these fungi can also live saprophytically on dead organic matter, and they can attack other fungi (mycoparasites) and colonize plant roots as endophytes (Nordbring-Hertz *et al.* 2006). These fungi described below (Hyde *et al.* 2014), are divided into four groups depending on their mechanism of action. The nutrients obtained by the fungi from the nematodes are used to form new fungal structures.

1) Trap forming fungi
These fungi form various types of trapping organs in their hyphae. There are two different mechanisms that function in the traps: adhesive and mechanical. Whatever the mechanism, the fungus can penetrate the cuticle of the nematode through the trap, forming a bulb of infection inside the nematode, from which the trophic hyphae grow inside the body and digest its contents (Nordbring-Hertz *et al.* 2006, Saumell *et al.* 2008, Mendoza-de-Gives and Valero-Cross 2009, Castañeda-Ramírez *et al.* 2016, Aguilar-Marcelino *et al.* 2017a, Mendoza-de-Gives 2020).

2) Endoparasitic fungi
Endoparasites use their spores to infect nematodes. These fungi are often forced parasites of nematodes, and they appear only as structures of dissemination outside the infected body of the nematode. The spores of these fungi adhere to and penetrate the cuticle of the nematode, thereby becoming embedded in it (Nordbring-Hertz *et al.* 2006, Zhang *et al.* 2011).

3) Ovicidal fungi
These fungi infect nematode eggs and produce appressoria (infection structures at the ends of the hyphae that attach to the egg cover). The fungi penetrate the egg cover and digest the contents (Nordbring-Hertz *et al.* 2006).

4) Toxin-producing fungi
The most common fungus in this group is the wood decomposer *P. ostreatus*, along with other species of the genus *Pleurotus*. This type of fungus contains a toxin in its hyphae; after contact with the toxin, the nematode is quickly immobilized. The fungal hyphae then grow chemotropically through the mouth of the nematode, digesting it, similar to the nematophagous fungi (Nordbring-Hertz *et al.* 2006).

The majority of these fungi belong to the basidiomycetes, for example, the genera *Pleurotus* and *Coprinus*; however, other fungi within the ascomycetes (*Lecanicillium*, *Paecilomyces*, and *Pochonia*) also produce nematicidal compounds. The fungus *Paecilomyces lilacinus* secretes acetic acid that paralyses young nematodes (Djian *et al.* 1991), and bioactive compounds have also been isolated from *in vitro* cultures of *Pochonia chlamydosporia*. Currently, more than 270 species

of fungi have been reported to produce nematicidal compounds (Zhang *et al*. 2011).

Coprinus comatus has been reported to immobilize the activity of *Panagrellus redivivus* via two strategies (Luo *et al*. 2007). The first is through spiny spherical structures (toxocysts) (Armas-Tizapantzi *et al*. 2019) that attract nematodes; when the toxocysts come into contact with the cuticle, they immobilize the nematode and the fungal mycelia invades the body and degrades it (Barron and Thorn 1987, Al-ani *et al*. 2020).

The second strategy involves the production of various products including toxins, such as ostreatin/trans-2-decanoacid, linoleic acid peroxide and extracellular proteases (serine proteases) (Kwok *et al*. 1992); proteins (Cuevas-Padilla 2019), such as ostreolysin, amatoxin, coprin, phaloxin and acromelic acid; and secondary metabolites, including cheimonophyllon E and 5-hydroxymethyl-furancarbaldehyde in *P. ferulae*, trans-2-decenedioic acid from *P. ostreatus*, and p-anisaldehyde, p-anisyl alcohol, 1-(4-methoxyphenyl)-1,2-propane-diol, 2-hydroxy-(4'-methoxy)-propiophenone, S-choriolic acid and linoleic acid from *P. pulmonarius* (Cuevas-Padilla *et al*. 2018, Pineda-Alegría *et al*. 2017, 2020, Castañeda- Ramírez *et al*. 2020).

IMPORTANT ASPECTS OF THE GENUS *PLEUROTUS*

Pleurotus spp.

White rot fungi, such as *Pleurotus* species, are considered primary decomposition agents because they are able to use agricultural waste in its original form (i.e., not previously subjected to any biochemical or microbiological degradation process) (Camacho-Morales *et al*. 2017). Several species of edible mushrooms are currently cultivated on an industrial scale. This provides an excellent alternative use for these fungi, as they grow abundantly on coffee pulp (*Coffea arabica*), sugar cane bagasse (*Saccharum officinarum*) and henequen (*Agave fourcroydes*), among other diverse lignocellulosic materials (Salmones and Mata 2012, Sánchez and Royse 2017).

Pharmacological studies of the genus *Pleurotus* have been carried out on different parts of the fungus, such as the fruiting body, also known as basidiocarp, carpophore or sporophore, and the mycelium, as well as from the degraded substrate. Different extracts and metabolites, such as phenolics, polypeptides, terpenes, sterols and polysaccharides, among others, have been obtained from the fungal materials described above (Ribeiro *et al*. 2006). Among these metabolites, the most studied are the polysaccharides obtained from the fruiting bodies and mycelia of several species, including *P. ostreatus*, *P. sajor-caju* and *P. citrinopileatus* (Gómez-Velázquez 2018).

Species of genus *Pleurotus* have different medicinal and therapeutic properties including anti-inflammatory (Smiderle *et al*. 2008, Gómez-Velázquez 2018), antihypertensive, cardiotonic (Gómez-Velázquez 2018), antiviral, antimicrobial, cytotoxic, antitumor, anticarcinogenic and antioxidant activities (Sánchez *et al*. 2015). Metabolites, such as lovastatin and others of phenolics, flavonoids and tannins, have been identified and isolated from edible wild mushrooms including *P. ostreatus* and *P. djamor*. Of the main phenolic compounds found in the genus *Pleurotus*, those derived from benzoic acid (gallic and syringic acid) and cinnamic acid (ferulic and caffeic acid) stand out (Oropeza 2017).

Based on their immunomodulatory activity, the fungi of the genus *Pleurotus* have been further studied as a natural source of bioactive compounds capable of complementing or stimulating a desired immune response in the host. These products include substances of high molecular weight, mainly polysaccharides of the type β-(1,3)-(1,6)-D-glucans, proteins, proteoglycans and polysaccharide-protein complexes, as well as different secondary metabolites of low molecular weight (Quevedo *et al*. 2018).

Insecticide activity has also been reported. Extracts from the species *P. ostreatus* have insecticidal properties against *Tribolium castaneum* and *Macrosiphum rosae*, with higher insect toxicity observed as the time of extract exposure increases (Pérez-Moreno *et al*. 2010). Another property of *P. ostreatus* is its ability to biodegrade organophosphate insecticides in the soil. This is because it secretes several extracellular enzymes that degrade a great variety of natural and anthropogenic compounds, which have chemical structures similar to lignin (Pino *et al*. 2019). *Pleurotus ostreatus* also has antiparasitic and anthelmintic (nematicide and cestocides) properties (Pérez-Moreno *et al*. 2010, Salmones and Mata 2012, Aguilar-Marcelino *et al*. 2017b).

Studies carried out by Thorn and Barron (1984) mention five species of *Pleurotus*, *Pleurotus strigosus*, *P. subareolatus*, *P. cornucopiae*, *P. cystidiosus* and *P. ostreatus*, which each present a different capacity to attack and consume nematodes, suggesting that the-

se fungi use the nutrients of their prey (nematodes) to complement the low levels of nitrogen available in wood. This mode of obtaining nutrition is similar in principle to that of the superior "carnivorous" plants. Hibbet and Thorn (1994) also indicated that the genus *Pleurotus*, *sensu* Singer, displayed a typical form of nematode capture that seemed characteristic of the genus; they suggested that this could be adequate for identifying members of the genus. They mention the positive activity of the species *P. cornucopiae*, *P. cystidiosus*, *P. levis*, *P. ostreatus*, *P. populinus*, *P. subareolatus*, *P. pulmonarius*, *P. dryinus*, *P. euosmus*, and *P. eryngii*. Additionally, Sharma (1994) reported that the breeding ground of *Pleurotus sajor-caju* can immobilize the nematodes of the mushroom *Agaricus bisporus* and more recently, the species *P. djamor* has also been reported to have anthelmintic activity (Pineda-Alegría *et al.* 2017).

The fungus *P. tuberregium* is a common basidiomycete found in tropical climates in Africa and Australia. Studies show that the sclerotia of this fungus are formed under the soil because the basidiocarpus has skeletal hyphae interspersed (Gilbertson 1981). Hibbet and Thorn (1994) reported the capture of the free-living nematode *Rhabditis* sp. by *P. tuberregium*. Cultivated in water-agar, the fungal mycelia produced toxin droplets, and when the nematodes came into contact with the toxin droplets, they became paralyzed and then colonized by the fungal hyphae. This mode of nematode capture has been previously demonstrated only in *Pleurotus* species genus, *sensu stricto*.

Regarding the nematicidal activity of the genus *Pleurotus*, several studies have been carried out on diffe-

short side stipe, which can sometimes be eccentric. The meat or context of the mushroom is white or whitish, with a pleasant taste and smell. The fruiting bodies grow in a gregarious manner and are generally overlapping on fallen or standing trunks, or on various plant remains. This fungus is distributed across the world in temperate and tropical forests (Salmones and Mata 2012).

The species *P. ostreatus* represents an alternative for parasite control in the livestock sector, as it has nematicidal activity against different taxonomic genera of nematodes that infect livestock (e.g., the eggs and infectious and histotrophic larvae of *H. contortus*), parasite nematodes of public health importance (e.g., *Ancylostoma caninum*) and free-living nematodes (e.g., *Panagrellus redivivus*) (Garcia-Lopes *et al.* 2015, Sanchez and Royse 2017).

The mechanism of action of edible mushrooms, particularly *P. ostreatus*, is carried out by structures known as "toxocysts" (Armas-Tizapantzi *et al.* 2019), which produce a nematotoxin called NRRL 3526 that acts against the bacteriophage nematode *P. redivivus*. At a concentration of 300 ppm, this toxin can induce 95 % lethality in these nematodes in one hour (Kwok *et al.* 1992). The fungal mycelia invade the body orifices, such as the anus and the mouth of the nematode, feeding on the body to obtain nutrients and continue their biological cycle. Trans-2-decenedioic acid is produced by *P. ostreatus* and is among the secondary metabolites responsible (Kwok *et al.* 1992).

Several studies have reported up to 84 metabolites isolated from *P. ostreatus* with nematicidal activity (Degenkolb and Vilcinskas 2016, Kwok *et al.* 1992). In addition, other compounds with nematicidal activity have been identified, such as alkaloids, quinones, peptides, terpenoids, fatty acids (e.g., pentadecanoic acid, palmitic acid, sitosterol and linoleic acid), and polyphenols (Li and Zhang 2014, Pineda-Alegría *et al.* 2020). However, other species of fungi, such as *Neolentinus ponderosus* and *Lentinula edodes* (Montañez-Palma 2020), also have great potential in the search for bioactive products with nematicidal activity in the livestock arena.

Pleurotus ostreatus has been reported to produce a nematotoxin that can immobilize nematodes in a few minutes; however, the mechanism of action by which this paralysis occurs had not been established for this fungus-nematode interaction. Additionally, other studies have investigated the predatory relationship between free-living nematodes (Diplogastridae) and *P. ostreatus* as a potential method of exterminating other parasitic nematodes of plants, animals and public health importance. After nematode invasion, the fungus *P. ostreatus* defends itself by causing the nematode's head to shrink. This phenomenon suggests that this anti-nematode mechanism is associated with linoleic acid peroxide (Satou *et al.* 2008).

Lee *et al.* (2020) conducted a study showing that *P. ostreatus* paralyses the free-living nematode *Caenorhabditis elegans* through a mechanism that is evolutionarily conserved in different nematode species. They found that the sensory "cilia" of *C. elegans* triggered a massive influx of intracellular calcium and a hypercontraction of the muscles in the pharyngeal wall and body, which eventually induced necrosis of the neuromuscular system throughout the nematode's body.

Secondary metabolites of the genus *Pleurotus* and their activity against gastrointestinal nematodes

To date, various compounds with nematicidal activity have been isolated from fungal hyphae, including alkaloids, quinones, peptides, terpenoids, fatty acids, and polyphenols (Li and Shah 2014). This activity against nematodes is of great importance from the agricultural and livestock point of view, as well as in the biocontrol of pests since their action against phytopathogenic insects and fungi has also been mentioned. These characteristics make them excellent candidates as natural biocontrol agents.

The secondary metabolites responsible for this action include trans-2-decenedioic acid, produced by *P. ostreatus*, and s-coriolic acid, linoleic acid, p-anisaldehyde, p-anisyl alcohol. However, the importance of these metabolites is questionable, as it has been shown that they are produced only in specific areas of the hyphae, and morphological differentiation to form specialized structures, called toxocysts, has only been shown in a few cases (Armas-Tizapantzi *et al.* 2019).

Several studies have reported the anthelmintic activity of *Pleurotus* species. A work carried out by Cuevas-Padilla *et al.* (2018) demonstrated the *in vitro* effects of a bioactive fraction from *Pleurotus* species. This bioactive fraction was evaluated against several stages of *H. contortus,* and it was shown that *P. ostreatus* had a higher nematicidal activity than *P. eryngii*. Later, Cue-

vas-Padilla (2019) carried out an *in vitro* evaluation of the proteins in raw extracts of five *Pleurotus* species (*P. cornucopiae*, *P. djamor*, *P. eryngii*, *P. ostreatus* and *P. pulmonarius*). The highest activity was obtained with *P. pulmonarius*, which was 81.2 % lethal against *H. contortus* eggs. They also revealed lethal effects against L_1, L_3 and L_4, as well as mobility inhibition.

Comparisons between the different types of activities (i.e., paralysis by the raw extract, inactivation by the extracts, and a hydroalcoholic extracts) suggested the involvement of products of a proteinaceous nature. These results demonstrated the nematicidal potential of putative *Pleurotus* species. proteins against *H. contortus* larvae. Arteaga-Paredes (2018) demonstrated the nematicidal and nematostatic potential of *P. ostreatus in vitro* against *Globodera pallida* larvae (J_2), a phytopathogenic nematode that generates losses of up to 30 % in potato crop yields (*Solanum tuberosum*) in Ecuador.

The nematicidal and nematostatic activity of the filtered broth of *P. ostreatus* was studied over time (8, 12 and 24 h) and at four different concentrations (0, 50, 75 and 100 %). The results showed that the percent mortality was directly proportional to the filtrate concentration and the exposure time. The most effective combination was a concentration of 100 % for 24 h, which resulted in a mortality rate of 41.6 %; treatment with a concentration of 100 % for 8 h resulted in the highest percent of immobilized nematodes (65.2 %). In another study (Aldaz 2018) it was reported that the fungus *P. ostreatus* has nematicidal activity. They initially obtained an extract using two solvents, acetone and methanol, through a Soxhlet extraction method. The nematodes used in these bioassays were *Ditylenchus dipsaci* and *Panagrellus redivivus*.

The acetone extract at a concentration of 75 % induced 95 % mortality in *D. dipsaci* and 92.55 % mortality in *P. redivivus*. Another study reported by Pineda-Alegría *et al.* (2017) evaluated the *in vitro* activity of extracts and fractions of *P. djamor* against *H. contortus* eggs and L_3 larvae. The results showed that most of the *P. djamor* extracts had no significant activity against the eggs; however, one extract induced 77-98.7 % mortality in L_3 larvae at 72 h post confrontation. Elucidation of the extract revealed several compounds including four fatty acids (pentadecanoic, hexadecenoic, octadecadienoic, and octadecanoic acid, and a terpene identified as β-sitosterol).

CONCLUSIONS

Edible mushrooms of the genus *Pleurotus* produce secondary metabolites with anthelmintic activity against gastrointestinal parasites in their larval stages. There is excellent potential in this fungal genus for biotechnological applications due to its biocontrol characteristics. There are new lines of research that should be addressed to demonstrate its effectiveness in the livestock arena, since metabolites and other compounds with anti-helminthic activity have been found in the mycelium, basidiomata, and degraded substrates where *Pleurotus* species had been cultivated. Among these potential investigations, the molecular approach stands out, as it is expected to help answer several questions, such as the mode of action and the conditions that predispose the fungus-nematode relationship.

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