Invited review [Revisión invitada]

RESEARCH ON CHEMICAL COMPOUNDS FROM EDIBLE MUSHROOMS FOR THE CONTROL OF GASTROINTESTINAL NEMATODES AND PHYTOPARASITES †

[INVESTIGACIÓN SOBRE COMPUESTOS QUÍMICOS DE HONGOS COMESTIBLES PARA EL CONTROL DE NEMATODOS GASTROINTESTINALES Y FITOPARÁSITOS]

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SUMMARY

Background: There are over 1,500,000 species of mushrooms worldwide and approximately 20,000 of them are present in Mexico where native cultures use some species of wild mushrooms for different purposes. Among those mushroom species approximately 200 are edible, the genus *Pleurotus* spp the second most produced and consumed on the American continent. The production of *Pleurotus* spp. have had rapid development in the food industry, due to their nutraceutical and pharmacological properties, ease of growth and adaptation to the diversity of organic substrates on wich they can grow. Other edible mushrooms, such as *Lentinula edodes* (Shiitake), have also been used for their nutraceutical properties. **Objective**: The present work provides a general and updated overview of the advances in the use of the secondary metabolites of edible macromycetes and their by-products for the control of parasites in the agricultural sector. The methodological strategy used was a detailed bibliographic review in different sources such as PubMed for the National Center for Biotechnology Information (NCBI), ResearchGate, Scopus, Science direct, among others. **Main findings:** The review process showed that nine species of edible mushrooms exhibited *in vitro* nematicidal activity against parasitic nematodes of plants (*Nacobbus aberrans* and *Meloidogyne enterolobii*) and

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animals (*Haemonchus contortus*), including *Pleurotus* spp (*P. ostreatus*, *P. djamor*, *P. eryngii*, *P. pulmonarius*, *P. cornucopiae*), *Lentinula edodes* (Shiitake), *Panus* sp, *Coprinus comatus* and *Hericium erinaceus*. The antiparasitic effect has been attributed to diverse chemical compounds such as fatty acids, polyphenols and terpenes, which have been isolated from macromycetes and their by-products (degraded substrates of macromycetes). Our research group has pioneered the study of the uses and applications of secondary compounds derived from edible mushrooms and their by-products for parasite control in the agricultural sector. **Conclusion:** This work sought edible mushroom products with nutraceutical potential that can satisfy the demands of producers and contribute to food self-sufficiency in Mexico.
Key words: edible mushrooms; agroindustrial by-products; phytoparasites; gastrointestinal nematodes.

RESUMEN

Antecedentes: A nivel mundial existen más de 1,500,000 especies descritas de hongos, de las cuales 20,000 de ellas se encuentran presentes en México. La mayoría corresponde a especies silvestres que son ampliamente utilizadas por la población nativa para diferentes propósitos. Entre estas especies de hongos aproximadamente 200 son comestibles siendo el género *Pleurotus* spp. el segundo más producido y consumido en el continente americano. Estos hongos han tenido un rápido desarrollo en la industria alimentaria, debido a sus propiedades nutracéuticas y farmacológicas, su facilidad de crecimiento y adaptación, y la diversa variedad de sustratos orgánicos en los que son capaces de crecer. Sin embargo, otros hongos comestibles como *Lentinula edodes* (Shiitake), también se han utilizado por sus propiedades nutracéuticas. **Objetivo:** El presente trabajo proporciona una visión general y actualizada de los avances en el uso de los metabolitos secundarios de los macromicetos comestibles y sus subproductos para el control de parásitos en el sector agrícola. La estrategia metodológica utilizada fue una revisión bibliográfica detallada en diferentes metadatos como PubMed para el National Center for Biotechnology Information (NCBI), ResearchGate, Springer, Elsevier, MDPI, Scopus, Science direct, entre otros. **Hallazgos principales:** El proceso de revisión mostró que nueve especies de hongos comestibles exhibieron actividad nematicida *in vitro* contra nematodos parásitos de plantas (*Nacobbus aberrans* y *Meloidogyne enterolobii*) y animales (*Haemonchus contortus*), incluyendo *Pleurotus spp* (*P. ostreatus*, *P. djamor*, *P. eryngii*, *P. pulmonarius*, *P. cornucopiae*), *Lentinula edodes* (Shiitake), *Panus* sp, *Coprinus comatus* y *Hericium erinaceus*. El efecto antiparasitario se ha atribuido a diversos compuestos químicos como ácidos grasos, polifenoles y terpenos, que han sido aislados de macromicetos y sus subproductos (sustratos degradados de macromicetos). Nuestro grupo de investigación ha sido pionero en el estudio de los usos y aplicaciones de compuestos secundarios derivados de hongos comestibles y sus subproductos para el control de parásitos en el sector agrícola. **Conclusión:** Este trabajo busco productos de hongos comestibles con potencial nutracéutico que puedan satisfacer las demandas de los productores y contribuir a la autosuficiencia alimentaria en México.
Palabras clave: hongos comestibles; subproductos agroindustriales; fitoparásitos; nematodos gastrointestinales.

INTRODUCTION

Sheep farming in Mexico has been affected by gastrointestinal nematodes (GIN) infections, which may damage grazing sheep's health and quality of life, leading to economic losses. A variety of factors can lead to an increase or decrease in the chances of severe GIN infections, including the environmental conditions and climate change, the vegetation present in the grazing paddocks, the animals' features and the animal husbandry practices (Bautista-Garfias *et al.*, 2022). The most prevalent nematode worldwide is *Haemonchus contortus*, found in tropical and subtropical regions (Fernandes *et al.*, 2019). These GIN have conventionally been controlled using commercially available drugs such as macrocyclic lactones (e.g., ivermectin; Emery *et al.*, 2016). Similarly, the agricultural sector has also been affected by phytoparasites, belonging to three orders: Tylenchida, Dorylaimida, and Tryplonchida. These nematodes are characterized by their stylets, which they employ to obtain nutrients from plants. Such nematodes are the so-called root nodulators or root galls, e.g., *Nacobbus aberrans* and *Meloidogyne enterolobbi*, (Martinez-Gallardo *et al.*, 2019). These parasites, may produce deformations in the root systems presenting nodules due to hyperplasia and hypertrophy. Also, the efficiency of the translocation of water and nutrients can be disturbed by a mechanical obstruction, thereby developing chlorosis, and wilting of plant leaves (Manzanilla-López *et al.*, 2002). These galling nematodes have traditionally been controlled with chemicals such as aldicarb, enzon, oxamyl, and cadusafos in 6 to 8 ppm (Soltani *et al.*, 2013).

The irrational use of anthelmintic (AH) products has led to the problem of anthelmintic resistance worldwide. Additionally, the activity of commercial AH drugs can damage beneficial organisms such as nematophagous mites (*Caloglyphus mycopaghus*; Quintero-Elena *et al.*, 2021) and dung beetles which are key in contributing to the organic matter returning part of its energy and nutrients to ecosystems, closing the life cycle (Basto-Estrella *et al.*, 2014; Cultid-Medina *et al.*, 2022). Due to the problems generated by the frequent use of agrochemicals, in agriculture and production and animal health, it is important to identify other sustainable alternatives for controlling of parasitic nematodes implicated. In this context, edible mushrooms have been shown to act as biocontrol

agents with antiparasitic activity associated with a vast repertoire of secondary compounds such as fatty acids, terpenes, and polyphenols, among others (Castañeda-Ramírez *et al.*, 2020). This paper provides an overview of the advances in using chemical compounds isolated from edible macromycetes and their by-products for the control of nematode parasites that affect animals (GIN) and plants.

Taxonomy of edible mushrooms

Approximately 120,000 species of mushrooms have previously been described worldwide. However, several studies have estimated that this number may reach up to 1.5 million species (Mata and Salmones, 2021). Over 2,000 species of fungi are considered safe for human consumption. Among the latter, 700 species are characterized for possessing some type of pharmacological property (Mata and Salmones, 2021).

The macromycetes fungi are edible mushrooms, among which species stand out, including *Lentinula edodes*, *Auricularia* spp., *Pleurotus* spp. (*P. ostreatus*, *P. djamor*, *P. eryngii*, *P. cornucopiae*, *P. cystidiosus*, *P. strigosus*, *P. subareolatus*, *P. florida*, and *P. ferulae*), and *Agaricus blazei* due to their large-scale production worldwide (Kalac, 2016).
Most of the research on edible mushrooms and their potential as parasite control tools for the agricultural sector has been performed mainly in the state of Chiapas, México, and exhibits great mycological diversity. The following are the characteristics of the macromycetes collection of the database from El Colegio de la Frontera Sur (ECOSUR): 6001 records of specimens/collected, 61 families, 156 genera, 252 species; 2238 records of specimens determined to the genus level, 3763 records of specimens determined to the species level, 1 national collection, 132 sites, 129 georeferenced localities, 6001 records of specimens associated with localities and georeferenced, and 305 associated photographs (Sánchez *et al.*, 2016).

Using natural enemies as biocontrol

Biocontrol can be defined as the mechanisms by which humans use one antagonistic organism to reduce another, e.g. parasitic populations in grasslands, plants, animals, to an acceptable sub-clinical level, while maintaining these populations at a non-harmful level. Thus biocontrol is generally considered to be managing a pest through the deliberate use of living organisms (Larsen, 2000; Lazarovits *et al.*, 2007).

Natural enemies that can help maintain parasite populations at acceptable levels include bacteria, viruses, protozoa, fungi, insects, mites and nematode predators of other nematodes (Aguilar-Marcelino *et al.*, 2012; Aguilar-Marcelino *et al.*, 2020; Sachman-Ruíz *et al.*, 2022; Al-Ani *et al.*, 2022; Quintero-Elena *et al.*, 2022). The following section describes some of the most studied microorganisms at the Centro Nacional de Investigaciones Disciplinarias, Salud Animal e inocuidad (CENID-SAI), belonging to the Instituto Nacional de Investigaciones Forestales Agricolas y Pecuarias (INIFAP) in México.

Fungi (micromycetes and macromycetes)

Nematophagous fungi are considered to be one of the main natural enemies of nematodes. Approximately 700 species of nematophagous fungi are known (Zhang *et al.* 2011). Indeed, these fungi can develop specialized organs to capture and destroy nematodes (Duddington, 1955). Their rings, branches, conidia, and adhesive spores enable the capture and later digestion of the parasites (Barron, 1977). Different species of these fungi have been evaluated *in vitro*, revealing their predatory potential against infective larvae of ruminant parasitic nematodes (Mendoza de Gives, 2011). *In vivo* studies in ruminants have yielded promising results on using *Duddintonia flagrans* and their chlamydospores. The latter possess the ability to resist and survive the passage through the gastrointestinal tract of ruminants, appearing in the feces where they create a mycelium that can achieve a reduction in the number of gastrointestinal nematode larvae (Aguilar-Marcelino *et al.*, 2017).

The macromycetes fungi have been shown to have a variety of medicinal properties. This has been evoked for centuries in the Chinese culture. The medicinal properties suggested or confirmed include immunomodulation, antiviral, antioxidant, antibacterial, and nematicidal (Cohen, *et al.*, 2002; Robaszkiewicz, *et al.*, 2010). Macromycetes exhibit great diversity. Those evaluated for their nematicide activity belong to the basidiomycetes group.

Several *in vitro* evaluations have been performed against parasitic nematodes of animals and plants, showing different AH effects (Table 1). Those effects have been attributed to other molecules present in the mushrooms which have been reported from the toxins and fatty acids associated (Castañeda-Ramírez *et al.*, 2020). From several species of mushrooms with potential nematicide activity, the most studied remains the genus *Pleurotus*. These have been reported to paralyse nematodes, leading to their subsequent death (Kwok *et al.*, 1992). Also, their by-products, such as mycelium, basidiomes, and degraded substrates, have been investigated for their nematicidal activity (Valdez-Uriostegui *et al.*, 2021).

Bioprospection of natural products

A bioprospection process involves taking a benefit from any natural product. Traditional medicine has been used in many cultures and countries to gain or

help maintain the health of individuals. Therapies developed in traditional medicine mainly consist of the administration of infusions or plant extracts but also can include a mixture of beliefs, practices, and knowledge based on the use of plants, animals, or minerals (Pereyra-Elías and Fuentes-Delgado, 2012). In traditional medicine, the plants with AH bioactivity are not necessarily consumed by humans or animals. On the other hand, there is an emerging interest in using of plants as nutraceutical materials (Hoste *et al.*, 2015). The latter refers to plants consumed by humans or animals that contain secondary metabolites beneficial to health and can contribute to individuals' nutrition (Waller *et al.*, 2001).

Many plant species are known to contain secondary metabolites exhibiting biological activity against parasitic nematodes (Hoste *et al.*, 2015). In addition, recent studies confirmed that several plant species consumed by small ruminants in the tropical forest of México can display biological activity against gastrointestinal nematodes (González-Pech *et al.*, 2015; Ventura-Cordero *et al.*, 2017 y 2018; Torres-Fajardo *et al.*, 2019; González-Pech *et al.*,2021; Ortíz-Domínguez *et al.*, 2022). The plants studied have included some species of legumes, which can be found during different times of the year, and which have shown activity against the eggs, infective larvae (L_3) and even adult stages of *H. contortus* (Torres-Fajardo *et al.*, 2021).

A bioprospection process has been performed on several species of *Pleurotus* spp. (*P. ostreatus*, *P. djamor*, *P. eryngii*, *P. pulmonarius*, *P. cornucopiae*), *Lentinula edodes* (Shiitake), *Panus* sp., *Coprinus comatus* and *Hericium erinaceus.* All these fungi specimens were provided by the Cepario Micológico from El Colegio de la Frontera Sur (Sánchez *et al.*, 2016). Our research group at the CENID-SAI, INIFAP has performed preliminary *in vitro* evaluations of these ten edible mushroom strains against *H. contortus*, *N. aberrans* and *M. enterolobii* (Aguilar-Marcelino, 2018; Castañeda-Ramírez *et al.*, 2020; Cruz-Arévalo *et al.*, 2020; Pineda-Alegría *et al.*, 2021; Comans-Peréz *et al.*, 2021).

In vitro evaluations against GIN

The AH properties of plant extracts have mainly been determined through evaluation protocols developed for metabolite-rich plants. The descriptions of a wide variety of *in vitro* tests are available in several scientific articles and books related to the subject (Jackson and Hoste, 2010; Castañeda-Ramírez, *et al.*, 2018). The advantages of using *in vitro* tests include acquiring more knowledge on what is being evaluated, alongside having a controlled environment, repeatability, reproducibility, low cost, and ease of use. Therefore, to perform *in vitro* tests on edible mushrooms, the mycelium and its predation capacity, when exposed to nematodes are used (Comans-Perez *et al.*, 2021). The tests used to evaluate edible mushroom extracts have included larval motility (Cedillo, 2016), egg hatching inhibition (Pineda-Alegria *et al.*, 2017), and recently the exsheathment inhibition tests (Ambrosio-Bautista, *et al.*, 2023), all of them against *H. contortus*.

Egg hatching test (EHT)

This test is based on the incubation of the GIN eggs at different concentrations of the respective extract and determines the ovicidal effect of the latter as the percentage of hatching inhibition (Jackson and Hoste, 2010).

Infective larvae (L_3)

Another biological model that has been used to evaluate the nematicidal activity of edible mushrooms is the infective larva of *H. contortus*. It is important to mention that during this stage the larvae have a protective sheath which provides them protection against desiccation until the host ingests them. This sheath is eliminated when passing through the rumen of the host, allowing exsheathed larvae to enter the epithelium of the abomasum. If the appropriate conditions exist, it can develop to the larva fourth stage and continue its cycle. In this sense, the model referred to emulates the conditions in which the larva reaches the abomasum and uses the extracts obtained from the mushrooms to prevent the development of the larva and break its life cycle as described by Brunet *et al.* (2008).

The larval exsheathment inhibition test (LEIT) was developed specifically to determine the AH effect that plant extracts have against the larval exsheathment process (Jackson and Hoste, 2010). This test has also been used to explore the possible efficacy of different fungal extracts in the process and the potential effectiveness of other fungal extracts in larval exsheathment inhibition using L_3 larvae. The LEIT is more sensitive than the previously mentioned tests, but it presents several requirements that, if not controlled, can cause great variability among the results obtained. It is advisable to use larvae from two to five weeks of age to obtain better repeatability (Castañeda-Ramírez *et al.*, 2017). Otherwise, variations can be found on the 50% effective concentration (EC_{50}) of the extracts. Brunet (2008) have shown that this test could measure the ability of infective larvae to settle in the abomasum or small intestine. Several studies using the LEIT to evaluate edible mushroom extracts have been reported since 2014 (Table 1).

Table 1. Summary of *in vitro* evaluations performed in México using different extracts of edible mushrooms against *Haemonchus contortus*.

Species	Stage	Reference
Pleurotus ostreatus	Larvae	Arizmendi–López, 2014
P. djamor	Larvae	Rodríguez–Bámaca, 2014
P. ostreatus	Egg	Diaz-Rodriguez, 2015
P. ostreatus	Egg and Larvae	Cedillo, 2016
P. djamor	Egg and Larvae	Pineda-Alegría, *et al.*, 2017
Pleurotus spp.	Egg and Larvae	Cuevas-Padilla, 2019
P. eryngii	Egg and Larvae	Cruz-Arévalo *et al.*, 2020
P. ostreatus, P. eryngii, P. cornucopiae, Coprinus comatus, Panus sp., Lentinula edodes, L. boryanus	Larvae	Comans-Pérez *et al.*, 2021
P. djamor (degraded substrate of different harvesting time)	Larvae	Colmenares-Cruz *et al.*, 2021
P. djamor	Egg and Larvae	González-Cortázar *et al.*, 2021
P. ostreatus, P. eryngii, P. djamor	Larvae	Sanchez-Salgado *et al.*, 2021
P. ostreatus mycelium, basidiomes, degraded substrate	Egg and Larvae	Valdez-Uriostegui, *et al.*, 2021
Lentinula edodes	Egg and Larvae	Pineda-Alegría *et al.*, 2021
Neolentinus ponderosus	Larvae	Montañez-Palma, *et al.* 2021
P. ostreatus	Egg and Larvae	Paez-Leon *et al.*, 2022
P. ostreatus, P. djamor, L. edodes	Larvae	Ambrosio-Baustista *et al.*, 2023

Proteins of *Pleurotus* spp with nematocidal activity

Mushrooms of the genus *Pleurotus* contain proteins with nematicidal properties. Cuevas-Padilla (2019) evaluated the crude extracts of *P. ostreatus* and *P. eryngii* and identified AH activity against *H. contortus* eggs. Among the bioactive compounds, soluble proteins (13-150 kDa) were found and visualized using polyacrylamide gels. Extracts from five *Pleurotus* species (*P. cornucopiae, P. djamor*, *P. eryngii*, *P. ostreatus* and *P. pulmonarius*) were then investigated to identify the crude extracts with the highest activity against *H. contortus* eggs. The extract of *P. pulmonarius*, with a 81.2% activity, simultaneously revealed a lethal effect against hatched L_1 larvae of *H. contortus* (Comans *et al.*, 2021).

In vitro tests performed against the L_3 and L_4 stages indicated a nematostatic effect on actively feeding stages such as L_4 (51%). The contrasts between the nematostatic activity of the crude extracts and a hydroalcoholic extract suggested the participation of protein-like compounds as major active compounds, demonstrating the nematocidal potential of possible proteins of *P. ostreatus* against the larvae of parasitic species.

Nematocidal metabolites of *Pleurotus* spp reported and published by the CENID-SAI, INIFAP group

Several *in vitro* anthelmintic activity studies have been performed with edible mushrooms such as those mentioned in Table 1. The mushrooms showing significant AH activity were later submitted to respective bioguided chemical protocols. Such studies were carried out to identify the possible molecules responsible for this AH activity (Figure 1). Table 2 summarizes the studies where the possible secondary metabolites responsible for the AH activity were reported.

Bioactive fractions PdR2 and PdB of *Pleurotus djamor* against animal and plant parasites

González-Cortazár *et al.* (2021), performed bioguided chemical fractionation of the hydroalcoholic extract of *P. djamor* basidiomes against *H. contortus*. The PdR2 fraction was the most active, as it inhibited 82% of egg hatching and 80% of L_3 larval mortality at 20 mg/mL. A second fractionation step enriched this fraction, and the PdB fraction was obtained. This fraction showed 100% inhibition of egg hatching at 5 mg/mL, > 95% and > 97% of mortality against L_3 larvae and L_4 larvae, respectively, using 10 mg/mL. Finally, proton and carbon nuclear magnetic resonance determined that the fraction contained allitol and a terpene in a 9:1 ratio.

The nematocidal activity of the PdR2 fraction was recently evaluated against second-instar (J2) juveniles of *M. enterolobii*. The PdR2 fraction at concentrations of 0.132, 0.625, and 1.25 mg/mL achieved a similar effect to that of a commercial AH drug (levamisole, positive control), with mortality rates of 87.6, 84.5, and 86.3%, respectively (Gómez-Rodríguez *et al.*, 2022).

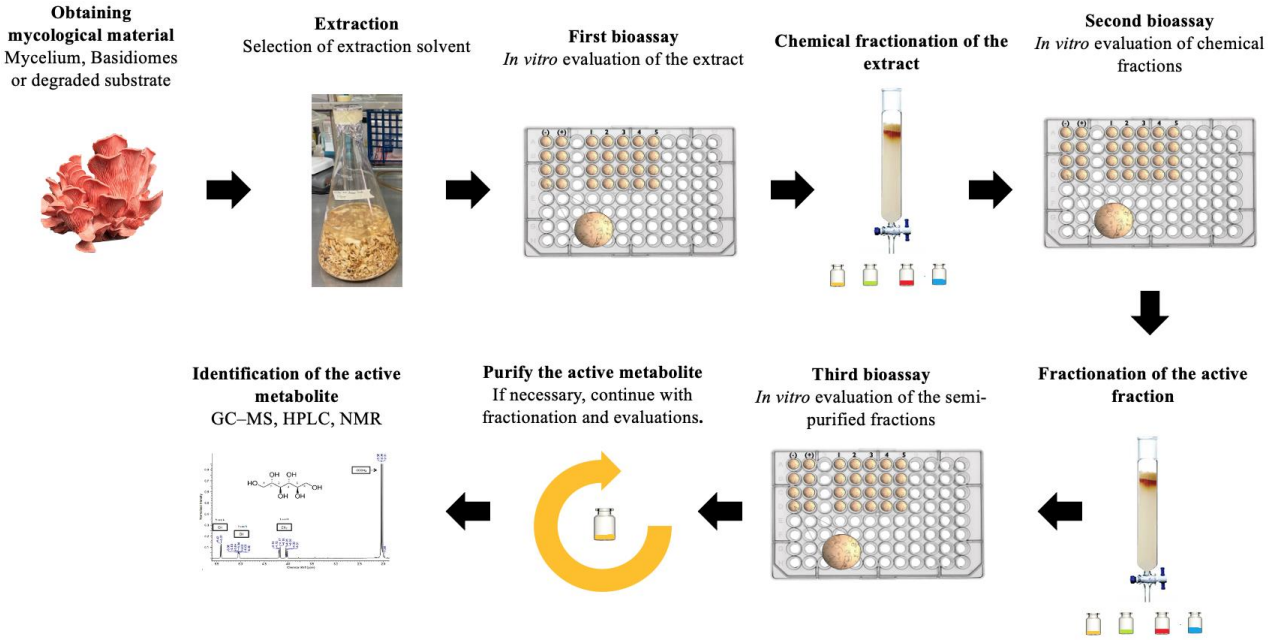

Figure 1. Diagram of the bioprospection process from edible mushrooms for identifying materials containing metabolites with nematocidal activity.

Table 2. Reports of secondary metabolites contained in the edible mushroom *Pleurotus* spp. against *Haemonchus contortus* evaluated by the CENID-SAI, INIFAP and collaborators.

Species	Compound	Reference
P. ostreatus	Xylitol **(1)** hexadecanoic acid **(2);** octadecanoic acid **(3)** ethanol 2-butoxy phosphate **(4)**; ethanol 2-butoxy phosphate (3:1) **(5)**	Cedillo, 2016
P. djamor	Pentadecanoic acid **(6)**; hexadecanoic acid **(2)**; octadecadienoic acid **(7)**; octadecanoic acid **(3)**; β-sitosterol **(8)**	Pineda-Alegría *et al.*, 2017
P. eryngii	Trehalose **(9)**; L-iditol **(10)**; galactitol **(11)**; D-mannitol **(12)**; D-glucitol **(13)**; Myo-inositol **(14)**; adipic acid **(15)**; octadecanoic acid **(3)**; Squalene **(16)**; β-sitosterol **(8)**	Cruz-Arévalo *et al.*, 2020
P. djamor (degraded substrate of different harvesting time)	Benzoic acid **(17)**; coumaran **(18)**; α-toluic acid **(19)**; *trans*-4-hydroxycyclohexanecarboxylic acid **(20)**; 2,6-dimethoxyphenol **(21)**; *cis*-cinnamic acid **(22)**; veratraldehyde **(23)**; veratryl alcohol **(24)**; *N*-phenylacetamide **(25)**; *p*-hydroxybenzoic acid **(26)**; isovanillic acid **(27)**; loliolide **(28)**; 4-hydroxy-3,5,5-trimethyl-4-[3-oxo-1- butenyl]-2-cyclohexen-1-one **(29)**; caffeine **(30)**; 5,6-dimethoxy-3H- isobenzofuran-1-one **(31)**; dibutyl phthalate **(32)**	Colmenares-Cruz *et al.*, 2021
P. djamor	Allitol **(33)**	González-Cortázar *et al.*, 2021
P. ostreatus	Vanillin **(34)**, β-sitosterol **(8)**, methyl *p*-hydroxycinnamate **(35)**, *p*-hydroxybenzaldehyde **(36)**	Paéz-León *et al.*, 2022

*The structural formulae of the compounds can be found in the appendix 1.

Mechanism of action of the chemical compounds obtained from edible mushrooms against nematodes of agricultural importance

One of the main mechanisms associated with the anthelmintic activity of the edible mushrooms *Pleurotus* spp (*P. ostreatus*, *P. strigosus*, *P. subareolatus* and *P. cornucopiae*) is the production of toxins called toxocysts from the mycelium of these mushrooms. When the toxocysts encounter the body of the nematodes directly, these worms become immobilized. This activity allows the fungal mycelium to enter through the nematode body's mouth, anus, and inter-cuticular areas. In this way, the mushroom can use nematodes as a feed source of feed supplying nutrients such as nitrogen (Armas-Tizapantzi *et al.*, 2019).

One study has previously identified the toxin *trans*-2-decenedioic acid. Its AH activity was lower than the corresponding simple fatty acid but higher than other dicarboxylic acids (Kwok *et al.*, 1992).

On the other hand, the secretion of laccases has also been suggested as a mechanism used by *Pleurotus* species to obtain nutritional resources from mainly free-living nematodes (*Rhabditis* sp) found sharing the same ecological niches (Armas-Tizapantzi *et al.*, 2019). The laccases belong to a group of enzymes called polyphenol oxidases containing copper atoms (also called multi-copper oxidases that oxidize polyphenols, aromatic diamines, and a range of other compounds). However, further studies are required to confirm this mode of action against parasitic nematodes of animals or plants.

***In vivo* tests using the gerbil model (*Meriones unguiculatus*)**

In vivo tests using the gerbil (*Meriones unguiculatus*) model have been carried out to evaluate the secondary compounds from edible mushrooms. In a study reported by González-Cortázar *et al.* (2021) performed a bioguided chemical fractionation of the hydroalcoholic extract of *P. djamor* basidiomes. The before mentioned PdB fraction showed a 92.56% reduction of *H. contortus* larvae *post-mortem*.

***In vivo* evaluations of sheep with GIN**

The good *in vitro* results against animal parasitic nematodes suggested the urgent need to evaluate different mushroom materials and by-products under *in vivo* conditions. Some *in vivo* evaluations of extracts, plants, and by-products have been carried out according to the recommendations suggested by working groups with expertise in the field (Sandoval-Castro *et al.*, 2012; Torres-Acosta *et al.*, 2012; Hoste *et al.*, 2015). In general, few studies have considered edible mushroom by-products with AH activity. Several challenges still need to be solved before any fungal materials or by-products can be used to control the parasitic nematodes of small ruminants. A key aspect will be to find a material that animals can willingly consume at sufficient quantity to allow the ingestion of sufficient secondary compounds that could exert its AH activity.

Metabolomics and molecular dynamics

Metabolomics has recently been used to facilitate the search for compounds derived from edible mushrooms with nematocidal activity (Pineda-Alegría, *in preparation*). This tool helps to the identification of active compounds, previously reported, present in extracts or fractions since it does not require the total purification of the samples (Kundu *et al.*, 2021). Thus, the amount of solvent to be used during the purification of the compounds is reduced, and their identification is facilitated (Paez-León *in preparation*).

On the other hand, studies are being carried out to determine the binding sites or mechanisms of action of the compounds that have been isolated from the different edible mushrooms, through techniques such as dockings and molecular dynamics. This is important because if the mechanism of action of these metabolites is elucidated, it will help to better understand how the metabolites act when in contact with nematodes and will provide more information for subsequent *in vivo* studies.

Challenges and perspectives

The main challenges in this research field involve elucidating the mechanisms of action of the different active metabolites, their synergism, or competition to display their effect. The application of the secondary metabolites from macromycetes and their by-products for the control of parasites in the agricultural sector and the generation of knowledge as basic science is very important, and we are currently using cutting-edge tools such as omics studies, specifically metabolomics, to study the metabolite profiles in mushrooms (Pineda-Alegría *et al.*, 2022).

Another challenging aspect is the development of technology for using secondary metabolites of mushrooms at large scale whether on agricultural or livestock industries.

CONCLUSIONS

Edible mushrooms and their by-products are a promising source of secondary compounds that can contribute to the control of parasitic nematodes of animals or plants. A well-protocolized methodology for their research has been acquired, and the recent

advances identified nine mushroom species with the potential for scaling their use at the industry level. Nevertheless, more research is needed to elucidate the different mechanisms of the leading chemical compounds involved in such AH activity. Also, the synergism, antagonism or competition among the different compound should be investigated. It is still necessary to develop the technologies that could be used to adapt the use of fungal materials at the farm level, aiming at the sustainable control of different parasites of animals and plants.

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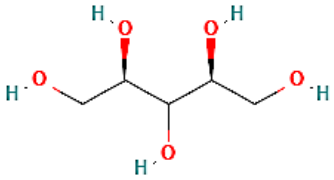
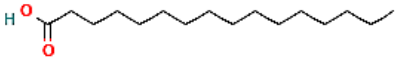
Appendix 1

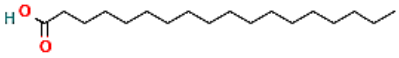
Structure of secondary metabolites contained in the edible mushroom *Pleurotus* spp. against *Haemonchus contortus* showed in table 2.



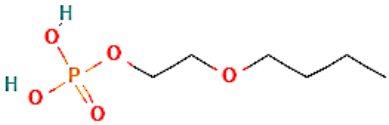
Xylitol **(1)**



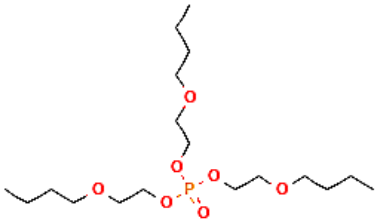
Hexadecanoic acid



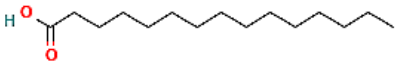
Octadecanoic acid **(3)**



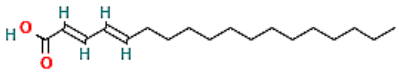
ethanol 2-butoxy phosphate **(4)**



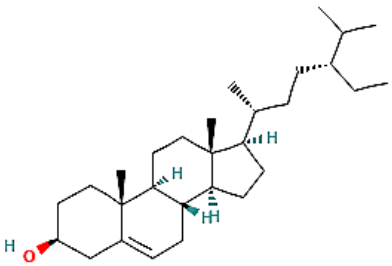
ethanol 2-butoxy phosphate (3:1) **(5)**



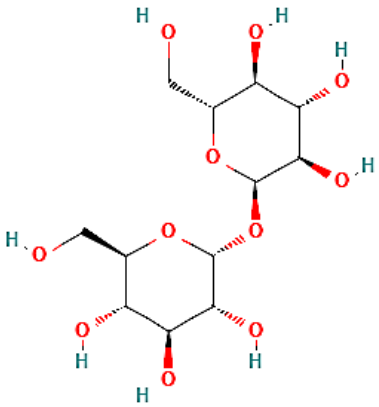
Pentadecanoic acid **(6)**



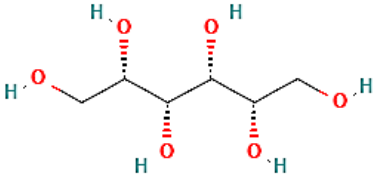
octadecadienoic acid **(7)**



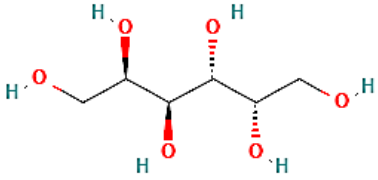
β-sitosterol **(8)**



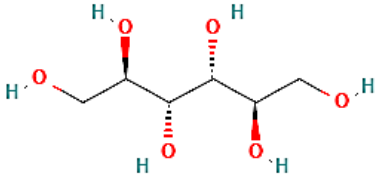
Trehalose **(9)**



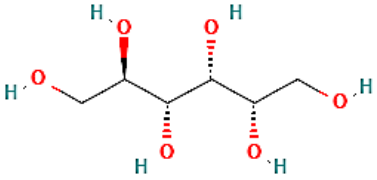
L-iditol **(10)**



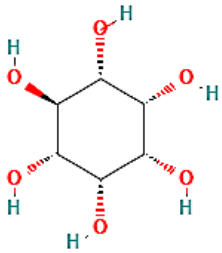
galactitol **(11)**



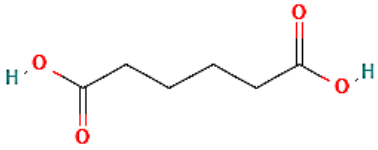
D-mannitol **(12)**,



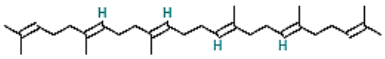
α-toluic acid **(19)**



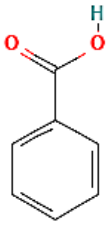
trans-4-hydroxycyclohexanecarboxylic acid **(20)**



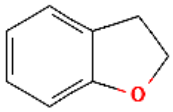
2,6-dimethoxyphenol **(21)**



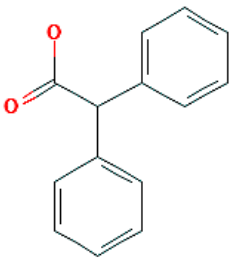
Squalene **(16)**

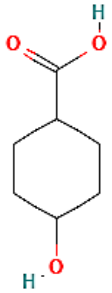


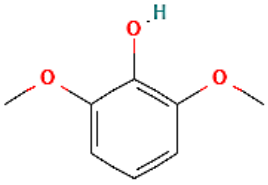
Benzoic acid **(17)**

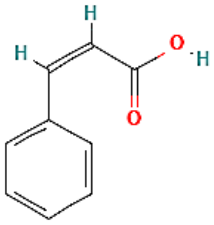


Coumaran **(18)**

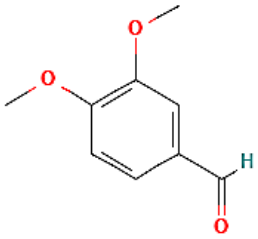




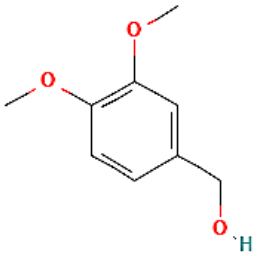




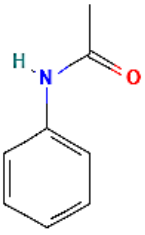
cis-cinnamic acid **(22)**



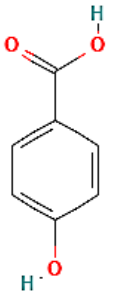
veratraldehyde **(23)**;



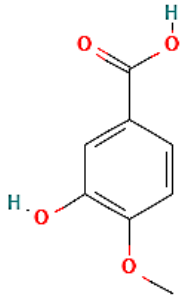
veratryl alcohol **(24)**



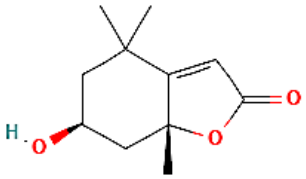
N-phenylacetamide **(25)**



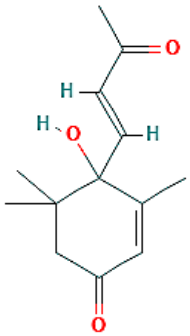
p-hydroxybenzoic acid **(26)**



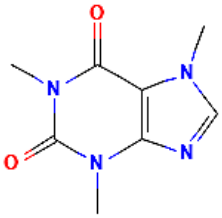
Isovanillic acid **(27)**



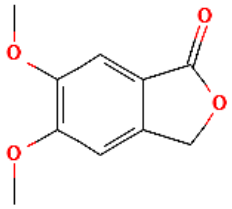
Loliolide **(28)**



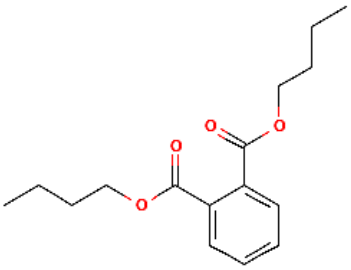
4-hydroxy-3,5,5-trimethyl-4-[3-oxo-1- butenyl]-2-cyclohexen-1-one **(29)**



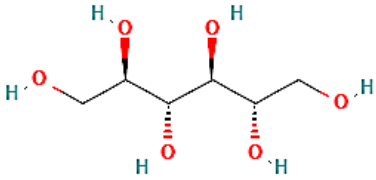
Caffeine **(30)**



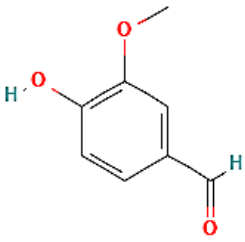
5,6-dimethoxy-3H-isobenzofuran-1-one **(31)**



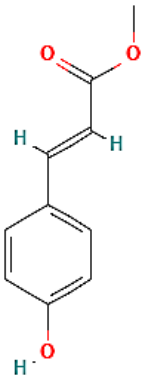
dibutyl phthalate **(32)**



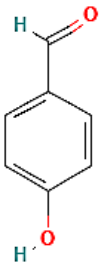
Allitol **(33)**



Vanillin **(34)**



Methyl-*p*-hydroxycinnamate **(35)**



p-hydroxybenzaldehyde **(36)**