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MINI-REVIEW

Bioherbicidal potential of different species of *Phoma*: opportunities and challenges

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Abstract

Modern agriculture has been facing new challenges and fostering innovations to establish sustainable plant production. An integral part of these strategies is implementing new eco-friendly technologies in plant protection for better human health and a safer environment by minimizing the use of hazardous chemicals and also encouraging innovations such as the use of bio-based strategies for weed control. This specific strategy addresses the need to reduce the use and risk of pesticides, replacing conventional chemical herbicides with new bio-based solutions. In response to these issues, biocontrol strategies are gaining increased attention from stakeholders such as farmers, seed companies, agronomists, breeders, and consumers. Among these, bioherbicides have huge potential for the management of harmful weeds without affecting the natural quality of the environment and human health. In this context, this review is devoted to present an overview of the mycoherbicidal potential of *Phoma sensu lato* group of fungi, examining the advances in this field, including technological and scientific challenges and outcomes achieved in recent years. The mycoherbicides are eco-friendly and economically viable.

Key points

- *Some Phoma species have demonstrated herbicide activity.*
- *These species secrete secondary metabolites responsible for the control of weeds.*
- *They can be used as non-chemical, cost-effective, and eco-friendly bioherbicides.*

Keywords Mycoherbicide · Bioherbicide · *Phoma* · Weed control · Eco-friendly · Economic viability

Introduction

Weeds are the most common and severe biotic factors that limit crop production and reduce the yield in quantity and quality. It has been estimated that 227 weed species are associated with 90% of crop losses in world agriculture. The global losses in the production of eight cash crops like cotton, coffee, soybean, rice, wheat, barley, maize, and potato due to weeds have been assessed to be $76.3 billion (Bailey 2014; Varah et al. 2020). Apart from the major role of weeds in agricultural production losses, they are the source of insects and pathogens, which attack crop plants. Furthermore, they destroy native habitats, threatening native plants and animals. To avoid continuous depletion of natural resources, achieve goals of sustainable agriculture development, and take into consideration the ill effects of chemical pesticides, various eco-friendly management strategies are needed for the management of weeds (Charudattan 2001; Chauhan 2020). Therefore, researchers all over the world are endeavoring continuously to search for new methods to tackle this problem. In the last decades, much attention has been paid on the application of biological control agents (BCAs) particularly fungi, including pathogens and endophytes, and biologically active secondary metabolites secreted by these microorganisms

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which are considered as the crucial opportunity to provide agriculture with effective tools for satisfactory crop production while minimizing impacts on health and the environment (Schwan-Estrada et al. 2000; Aneja 2009; Baque et al. 2012).

Phoma sensu lato constitutes an important source of secondary metabolites with high mycoherbicidal activity, as some species secrete bioactive compounds that are used in the control of weeds, causing lesions on leaves, stalks, flowers, and pods, as well as discoloration of the hypocotyl, cotyledon, and roots (Bailey et al. 2011a, b; Brun et al. 2016; Graupner et al. 2006; Todero et al. 2019). *Phoma* has always been considered by scientists as one of the most challenging fungal genera both due to complicated identity arising from unclear taxonomical borders and similarity of micromorphological characters (Saccardo 1880, 1884; Boerema et al. 2004; Aveskamp et al. 2010) and because of the tremendous diversity of species and ubiquitously occurring in the different ecological niches (Chen et al. 2015). Nowadays, *Phoma* belongs to *Didymellaceae*, which is considered one of the largest families in the fungal kingdom, including more than 5400 species belonging to at least 36 genera that have been recorded, comprising recently established genera such as *Neoascochyta* and *Paraboeremia* and historical ones such as *Ascochyta*, *Didymella*, and *Phoma* (Hou et al. 2020). The sequences tool turned out to be useful in re-classifying *Phoma sensu lato* clades, which made the taxonomical status clear. The species of *Phoma* are the gold mine of bioactive metabolites including the highly selective as well as less specific, with the great diversity acting like mycoherbicides (Rai et al. 2009; Rai et al. 2018).

This review offers an overview concerning *Phoma sensu lato* fungi in the prospect of mycoherbicidal application, summarizing the efforts of the research community on this topic and emboldening discussion on our joint priority of a healthy and sustainable environment.

Bioactive metabolites of *Phoma sensu lato* as mycoherbicides

Phoma sensu lato group of fungi includes several species that secrete bioactive metabolites having potential for the management of weeds leading to the development of lesions on leaves, stems, flowers, and fruits (Table 1). These species also damage the chlorophyll content leading to discoloration of cotyledons, hypocotyls, and seedlings (Bailey et al. 2011a, b; Hynes 2018).

Phoma macrostoma, one of the most examined species, mainly in Canada, has tremendous potential as a mycoherbicide as it has been reported to deteriorate the weeds. Hynes (2018) reported that *P. macrostoma* Montagne 94–44B is a remarkable mycoherbicide with high efficacy on the removal of broadleaved weeds such as dandelion (*Taraxacum officinale*). In 2016, The Pest Management Regulatory Agency (PMRA) of Canada has granted registration and permitted for use and sale of the bioherbicide *P. macrostoma* Montagne 94–44B, and now, it is available on a commercial scale on the market.

How does *P. macrostoma* infect the target weeds? It has been addressed by Bailey et al. (2011a, b). The mycelium of *P. macrostoma* can incite photobleaching and plant damage. In susceptible hosts, the fungus grows beside the trachea interfering with root cell structures. In resistant hosts, fungal growth is restricted to root hairs and epidermal layers. Generally, *P. macrostoma* occurs in soil and also as a phytopathogen. For the management of dandelion, the application of *P. macrostoma* 94–44B in soil resulted in the destruction of the weed. The authors also applied the inoculum of the test fungus *P. macrostoma* by foliar spray. They studied the root colonization after treatment of 7 and 28 days and found that symptoms of photobleaching in leaves of dandelion provide evidence of infection process of *P. macrostoma* after application of mycelium in granular formulations (Fig. 1). However, in soil application, only mycelium was found to be effective (Bailey et al. 2011a, b). The mycelium did not enter into the cell (Fig. 1) but formed an intercellular network and was responsible for the deterioration of the cortex due to secreting macrocidins (Graupner et al. 2003; Pedras et al. 2008). The macrocidins secreted by *P. macrostoma* affect the carotenoids of the leaves of dandelion. Hubbard et al. (2015) reported that the secondary metabolites produced by the fungus are responsible for the photobleaching effect; as a result, the synthesis of carotenoids is inhibited. The metabolites also reduce the chlorophyll content of the leaves. Till today, the mechanism of the photobleaching effect is still unknown, and therefore, there is a pressing need to elucidate this mode of action.

Optimization of mycoherbicide production by *Phoma*

There is a need for an economically viable process for the production of mycoherbicides (Klaic et al. 2017). In this context, many researchers suggested solid-state fermentation for the development of the process (Singhania et al. 2010; Klaic et al. 2017). In such a process, agricultural waste can be used for the development of substrates including rice husks, wheat bran, sugarcane bagasse, and soybean meal. Usually, the substrates are ground after fermentation and used with the granular formulation of herbicides. Klaic et al. (2017) reported that the bioherbicide prepared from *Phoma* sp. showed activity on the target plant. However, the efficacy of the bioherbicide depends upon the fermentation medium. The optimized conditions for the production of bioherbicide

Table 1 *Phoma* spp. used as mycoherbicides and target weeds

Phoma sp.[1]	Phytotoxic metabolites	Target weed	Reference
Phoma asparagi	Altiloxin A	*Asparagus*	Ichihara et al. (1984)
Phoma bellidis	Bellidisins A–D	*Tricyrtis maculata*	Wang et al. (2019)
Phoma betae	Betaenone A	*Beta vulgaris*	Ichihara et al. (1983)
Phoma chenopodiicola	Chenopodolans A–C	*Chenopodium album*	Cimmino et al. (2013a, 2013b)
	2-(3-Methoxy-2,6-dimethyl-7aH-furo[2,3-b]-pyran-4-yl)-butane-2,3-diol, 1-(3-methoxy-2,6-dimethyl-7aH-furo[2,3-b]-pyran-4-yl)ethanol and 3-methoxy-2,6-dimethyl-4-(1-methylpropen-yl)-7aH-furo[2,3-b]pyran		
Phoma chenopodiicola	3-(3-Methoxy-2,6-dimethyl-7aH-furo[2,3-b]-pyran-4-yl)-but-2-en-1-ol (chenopodolan D, 1) (1S,2S,3S,4S,5S,9R,10S,12S,13S)-1,3,12-tri-acetoxy-2,hydroxy-6-oxo-ent--pimara-7(8),15-dien-18-oic acid 2,18-lactone (chenopodolin B, 3), and, 4,5,7-trihydroxy-3-methyl-isochroman-1-one (chenisocoumarin, 2)	*Chenopodium album*	Evidente et al. (2015)
Phoma commelinicola		*Commelina diffusa*	Boyette et al. (2015)
Phoma destructiva		*Cirsium arvense*	Kluth et al. (2005)
Phoma exigua	Cytochalasins	*Cirsium arvense, Sonchus arvensis,*	Cimmino et al. (2008)
Phoma exigua		*Centaurea solstitialis*	Vidal et al. (2004)
Phoma exigua		*Acroptilon repens*	Tunali et al. (2003)
Phoma exigua	Deoxaphomin	*Sonchus arvensis*	Cimmino et al. (2008)
Phoma exigua var. *exigua*		*Taraxacum officinalis*	Stewart-Wade and Boland (2004)
Phoma exigua var. *exigua*		*Cirsium arvense*	Bithell and Stewart (2001)
Phoma herbarum FGCC 75	3-Nitro-1,2-benzenedi-carboxylic acid (3-nitrophthalic acid)	*Parthenium hysterophorus*	Vikrant et al. (2006)
Phoma herbarum	-	*Taraxacum officinale*	Neumann and Boland (2002)
Phoma herbarum		*Taraxacum officinale*	Schnick and Boland (2004)
Phoma herbarum		*Trianthema portulacastrum*	Ray and Vijayachandran (2013)
Phoma herbarum		*Parthenium hysterophorus, Lantana camara, Xanthium strumarium, Cassia tora, Hyptis suaveolens, Sida acuta* and *Antigonon leptopus*	Singh and Pandey (2019)
Phoma herbarum	Herbarumins-(7*S*,8*S*,9*R*)-7,8 -dihydroxy-9-propyl-5-nonen -9-olide (I); and (2*R*,7*S*,8*S*,9*R*)-2,7,8-trihydroxy -9-propyl-5-nonen-9-olide (II)	*Amaranthus hypochondriacus*	Rivero-Cruz et al. (2000)
Phoma lingam	Phomalirazine	*Brassica napus, B.campestris*	Pedras et al. (1989)
Phoma macrostoma	*Phoma macrostoma* and Thaxtomin A	*Broadleaf weeds*	Wolfe et al. (2016).
Phoma macrostoma	Macrocidins A, B	*Taraxacum officinale*	Graupner et al. (2003)
Phoma macrostoma	Macrocidins	*Turfgrass*	Hubbard et al. (2015)
Phoma putaminum	Putaminoxin	*Erigeron annuus*	Evidente et al. (1997)
Phoma recurvifoliae	Herbarumin II	*Yucca recurvifolia*	Seo et al. (2007)
Phoma sp. NRRL 25697	Phomadecalins A, B, D, and C Phomapentenone A	*Hypoxylon stromata*	Che et al. (2002)
Phoma herbarum FGCC#54	1-Hydroxy-4-(3,5-dimethyl-4-hydroxyphenyl) -pentan-3-one	*Parthenium hysterophorus, Lantana camara, Hyptis suaveolens, Sida acuta*	Kalam et al. (2014)
Phoma tropica	5-Hydroxyramulosin, 7-methoxycoumarin	*Fucus spiralis*	Osterhage et al. (2002)

[1] Species are reported according to the name used in the corresponding reference

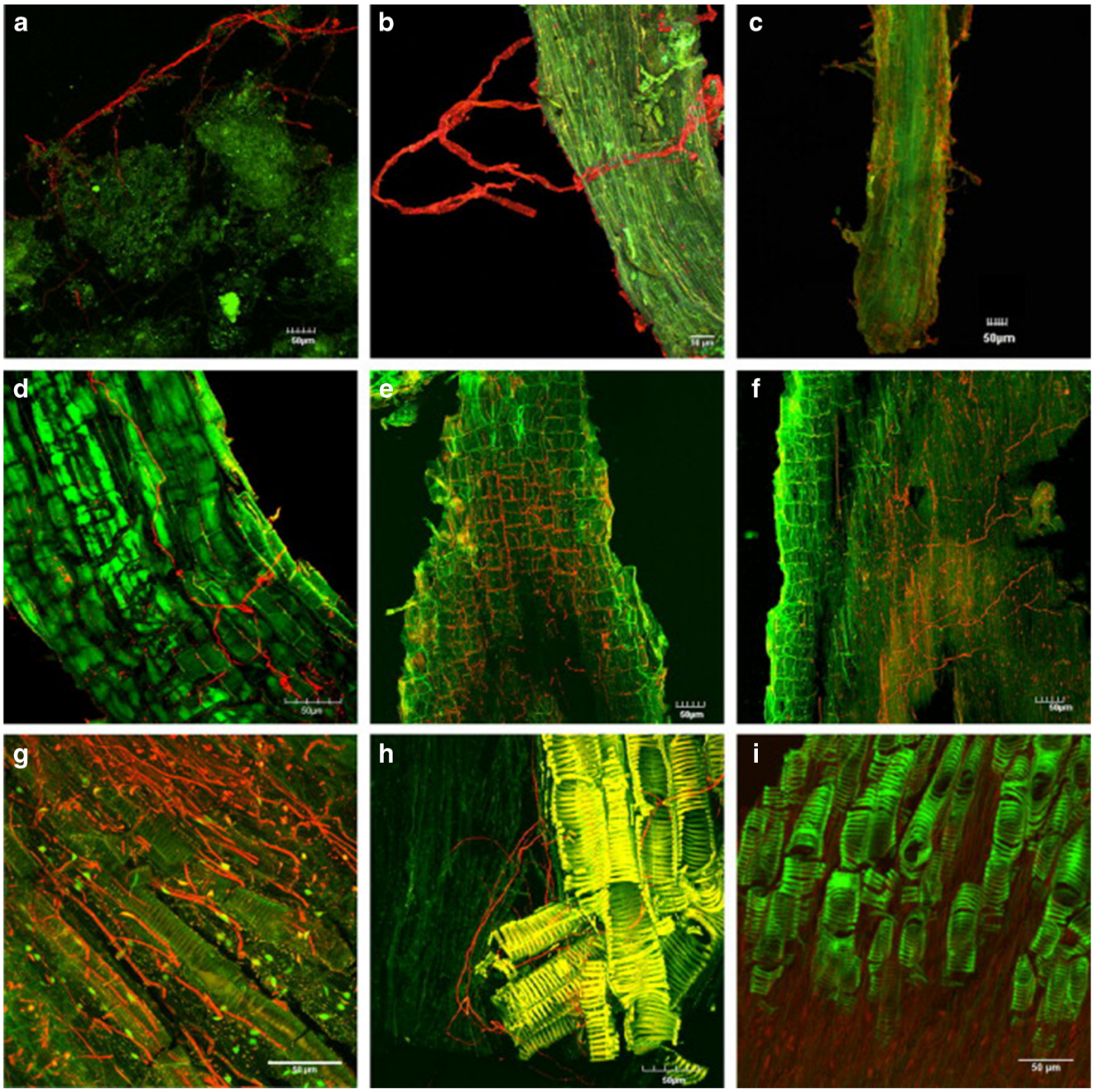

Fig. 1 Root colonization of dandelion (green) following inoculation with *Phoma macrostoma* 94-44B (red); **a** fungal mycelium proliferating from formulated granules, **b** growth and attachment of mycelium on dandelion root 7 days after treatment, **c** fungal mycelium associated with root hairs 7 days after treatment, **d** longitudinal section showing mycelial growth over and under interior root cell layers 7 days after treatment, **e** intercellular mycelial proliferation 28 days after treatment, **f** destruction of central core cell contents 28 days after treatment, **g** extensive mycelial proliferation parallel to the vascular trachea 28 days after treatment, **h** mycelial growth around but not penetrating trachea 28 days after treatment, and **i** lack of mycelial presence around vascular trachea in untreated dandelion 28 days after treatment. Images shown were stained with Pianese IIIB, except **b** which was stained using the antibody; reprinted from Bailey et al. (2011b) with permission from Elsevier

percentage by weight-wise (wt%) are moisture 70 wt%, soybean bran content 30 wt%, and Corn steep liquor (CSL) content of 20 wt% which is sufficient to cause 40% phytotoxicity. Finally, it is responsible for the reduction of carotenoids leading to chlorosis.

Formulation of mycoherbicide

There are reports that the formulations of bioactive metabolites obtained from microbial pathogens enhance the herbicidal activity of the product developed (Sica et al. 2016; Bastos

et al. 2017). In this context, Todero et al. (2018) evaluated the formulations of culture filtrate of *Phoma* without conidia, palm oil with Tween® 80, and Span® 80 for enhancement of toxicity to the target plants. The authors found that surfactant 2.8% weight per volume (w/v), palm oil concentration 8.2% (w/v), and hydrophilic–lipophilic balance of 12.8 were the optimum against three weeds including *Amaranthus retroflexus*, *Conyza canadensis*, and *Bidens pilosa*. The symptoms appeared after 48 h of the spray but varied in intensity on different weed species (Fig. 2). It is evident from the figures that symptoms on plants of *C. canadensis* were started from yellowing to necrosis. However, these symptoms were less intensive, while in the case of *A. retroflexus*, symptoms were more evident followed by necrosis (Fig. 3).

A. retroflexus demonstrated a substantial effect of formulation which was enhanced up to a greater extent in 15 days. The authors suggested that *Phoma* sp. have great potential as mycoherbicide. In the study by Brun et al. (2016), the authors used a stirred-tank reactor for fermentation to produce bioherbicide from *Phoma* sp. They used a 3L fermenter with a stirring rate that varied from 40, 50, and 60 revolutions per minute (rpm) and aeration of 1, 2, and 3 per volume of liquid per minute (vvm). The authors tested the effect of bioherbicide on *Cucumis sativus* and *Sorghum bicolor*. In the pre-emergence test, bioherbicide demonstrated 100% inhibition of both the species, while in the post-emergence test, phytotoxicity varied in *C. sativus* (25 to 66%) and *S. bicolor* (32 to 58%) (Fig. 4).

Effect of different factors on the efficacy of mycoherbicides

Concentration of the extract of *Phoma*

Generally, it has been found that the crude fungal extract of mycoherbicide with low concentration shows low herbicidal activity. Todero et al. (2019) studied the effect of different concentrations to enhance the activity of the bioactive compounds secreted by different *Phoma* spp. The authors concentrated the bioactive metabolites in microfiltration membranes, and the concentration of the crude extract was increased to 10, 30, 50, 70, and 90%. These concentrations were evaluated for their phytotoxicity on the juvenile leaves of *Cucumis sativus* and two weeds *Bidens pilosa* and *Amaranthus retroflexus*. Interestingly, the maximum herbicidal efficacy (80.7%) was found at 30% of the extract. The authors reported 100% control of the weeds when the evaluation was performed in the germination chamber.

Effect of temperature

The bioactivity of *P. macrostoma* is also governed by temperatures. Many of the previous studies have demonstrated that this fungus has shown optimal activity in cool climatic conditions (15–25 °C), while the control of slender aster (*Aster subulatus* var. *ligulatus*) at higher temperatures (27–31 °C) was reported by Smith et al. (2013). However, in another

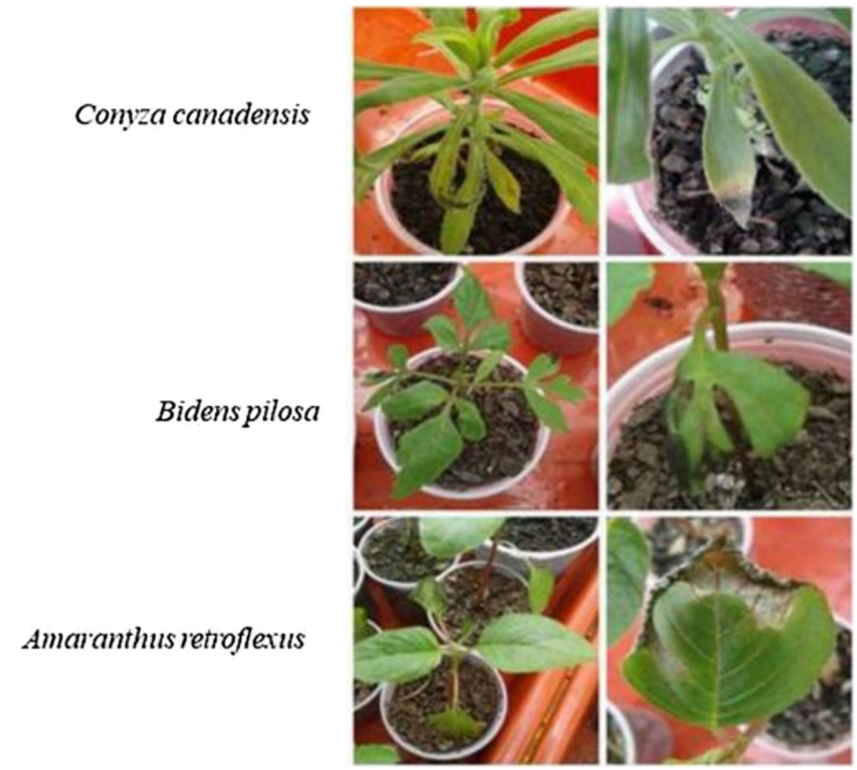

Fig. 2 Phytotoxic effects observed on *Bidens pilosa*, *Conyza canadensis*, and *Amaranthus retroflexus* at different intensities; reprinted from Todero et al. (2018) with permission from Elsevier

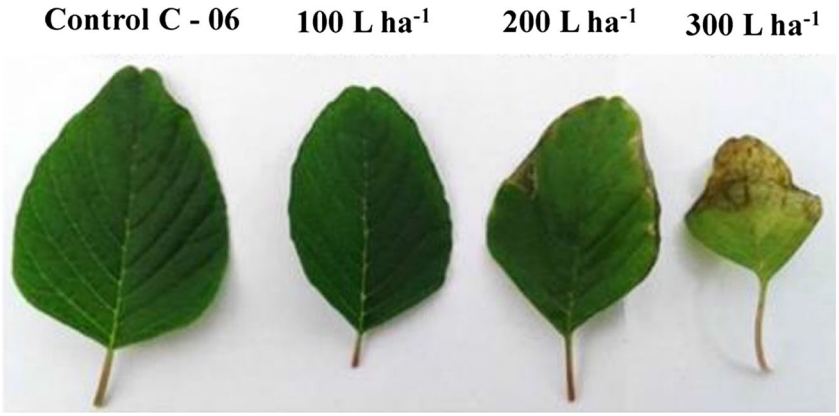

Fig. 3 Evolution of control on leaves of *Amaranthus retroflexus* using the formulation 06 sprayed at different flows and the Control C – 06 (0.82 g palm oil + 0.0576 g Span® 80 + 0.2224 g Tween® 80) sprayed at 100 L ha^{-1}; reprinted from Todero et al. (2018) with permission from Elsevier

comparative study, the authors found that *P. macrostoma* is more effective on dandelion compared to slender aster (Smith et al. 2015).

Effect of different fertilizers

In a study, Bailey et al. (2013) evaluated the effect of nitrogen, potassium, phosphorus, lime, and commercially used fertilizers along with mycoherbicide (*P. macrostoma*) and without herbicide against dandelion, and encouragingly, the authors found remarkable inhibition of dandelion from 70 to 100%. The authors reported that the combination of nitrogen (urea) remarkably destroyed the weed. On the contrary, phosphate, potassium, and lime did not show any effect on dandelion.

Fermentation process for the production of secondary metabolites of *Phoma*

In addition to the development of tools to identify and select microorganisms that produce secondary metabolites with the potential for biological control, it is necessary to establish the most appropriate bioprocesses and determine the best growth conditions for increasing the production of these compounds. Fermentation processes can be an alternative to produce

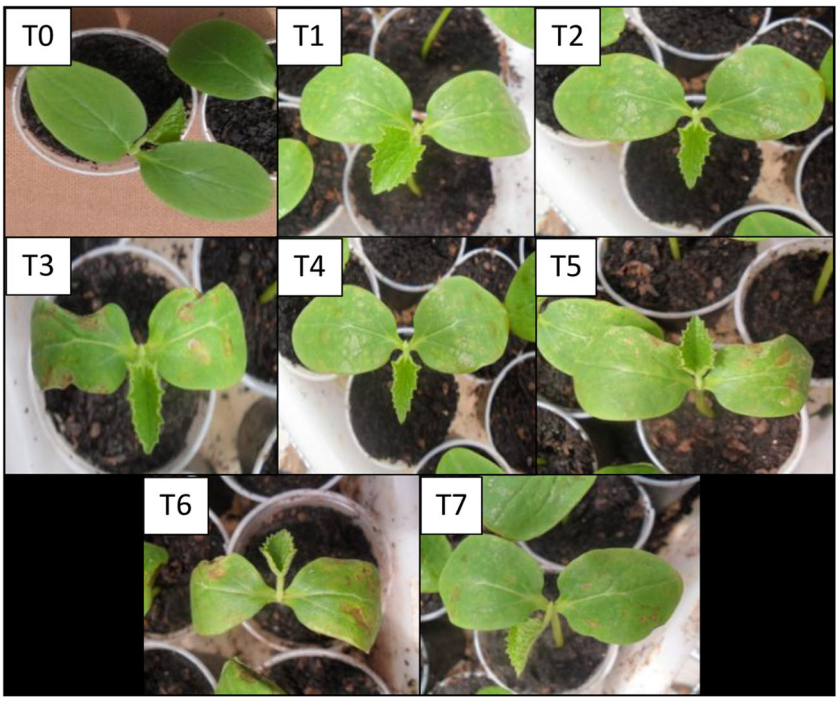

Fig. 4 Photograph illustrating the lesions caused by the fermented broth of *Phoma* sp. in *C. sativus*; reprinted from Brun et al. (2016); under Creative Commons Attribution 4.0 International License

secondary metabolites (Brun et al. 2016). Fermentation processes are labeled as a sum of steps or phases in which the culture media provide all the necessary nutrients. In a fermentative process, temperature, pH, agitation, and concentration of nutrients are controlled to offer favorable conditions for the growth of fungi. After the process, the fermented broth is subjected to the final treatment to separate products and by-products (Dernain 2006). The fermentation can be discontinuous, semi-continuous, or continuous, depending on the type of cultivation (solid or submerged cultivation) and the oxygen supply (aerated and non-plowed processes). Microbial processes are carried out in submerged fermentation or solid growth medium, the first being the most widely used on an industrial scale (Castro and Pereira 2010).

Solid fermented processes differ significantly from submerged processes in terms of sporulation and enzyme production, as well as in terms of mixing and diffusion. The submerged fermentation process proves to be relatively easy to cultivate on a large scale, since it ensures the homogeneity of the medium and easy control of the process parameters, especially if monitored by suitable sensors (Couto and Sanromán 2006; Daryaei et al. 2016b).

The higher production of biomass and secondary metabolites by fungi in fermentation processes is related to different factors, which involve the environment and growth conditions. Among these, the pH, the carbon/nitrogen ratio, and the mineral supplements as well as the physiological properties of the microorganisms (such as the age of the inoculum) are important factors. These factors must be carefully selected to optimize the growth and production process of secondary metabolites of endophytic fungi, maintaining viability and effectiveness (Gunasekaran and Poorniammal 2008; Daryaei et al. 2016a; Klaic et al. 2017).

Several studies have been carried out in recent years, to determine the fermentation process and the appropriate culture conditions for the greater production of the metabolites by endophytic fungi. When optimizing the submerged fermentation culture conditions to produce pigments by the fungus *Phoma herbarum* FGCC # 54, Quereshi et al. (2010) reported that the maximum production of biomass and metabolites was found at the ideal pH of the culture medium as 4.0. The authors also highlighted the viability of the commercial production of this pigment as a potential bioherbicide. Assessing the influence of the formulation of metabolites produced by the fungus *Diaporthe* sp. in solid-state fermentation with adjuvants, Bastos et al. (2017) found that fermentation in the solid state allowed the production of metabolites by the fungus *Diaporthe* sp. and observed that when formulated with adjuvants, there was an increase in the effectiveness of the bioherbicide against plants of *Cucumis sativus*.

The production of bioherbicides from *Phoma* sp. by solid-state fermentation was optimized by Klaic et al. (2017), using agro-industrial residues as substrate (sugar cane bagasse, soybean meal, and corn steeping water). These authors attested to high efficacy in the control of the target plant *C. sativus* and evidenced the achievement of a phytotoxicity level of 40 lesions. The intensity of the effect was influenced by the formulation of the fermentation medium. The best optimization conditions to produce bioherbicide were (% by weight) moisture content 70.0, soy bran content 30.0, and corn steeping water (CSL) 20.0.

The submerged fermentation of the fungus *Phoma* sp. in a bioreactor under controlled conditions of agitation and aeration was efficient, allowing an increase in biomass productivity, which shows that process optimization methods for the production of secondary metabolites of fungi with bioherbicide action are essential to increase the content of compounds (Brun et al. 2016). When evaluating the bioherbicidal activity of the fermented broth resulting from the submerged fermentation of the fungus *Diaporthe* sp. (*Lolium multiflorum*, *Conyza* sp., and *Echinochloa* sp.) in pre-emergence, Pes et al. (2016) evaluated the efficiency of fungal extract and found that there was 100% inhibition of the germination of all the studied species. In post-emergence, the growth of *Conyza* sp. and *Echinochloa* sp. was suppressed by the fermented broth.

A study was developed based on the use of a hollow fiber membrane to concentrate the fermented broth of *Phoma* sp. The objective was to increase the herbicidal activity in pre-emergence and post-emergence of the weeds *Bidens pilosa* and *Amaranthus retroflexus*. Pre-emergence had 100% control for both species. In the post-emergence, the control rate was influenced by the applied concentration of bioherbicide (Todero et al. 2019).

The biological control of weeds is one of the main challenges for organic and conventional agriculture. In this context, endophytic *Phoma* spp. produce a wide variety of secondary metabolites, which are still poorly investigated (Chaves Neto et al. 2019a, b, 2020a, b). The prospect for the near future is that more biocontrol products with high potential can be launched and marketed worldwide. Based on this, the technologies can be developed to concentrate and formulate secondary metabolites produced by endophytic fungi, and processes can be optimized for the development of large-scale productions.

Final considerations, challenges, and future perspectives

The tendency towards developing sustainable agriculture requires replacing chemical herbicides which result in a reduction of the biodiversity of natural enemies, an outbreak of weeds, development of herbicide-resistant weeds, and contamination of food and ecosystem. The biological agents are the promising alternatives for long-term control. Among

these, mycoherbicides play an important role and hence should be integrated with the weed management systems (Pyon et al. 2017; Aneja et al. 2017). However, to achieve better efficiency of mycoherbicides, there are some challenges such as changing environment, maintenance of shelf life and virulence of the formulation, and economic viability of the product.

There are still challenges about secondary metabolites produced by microorganisms, especially those produced by fungi. One of the challenges is low productivity, which is influenced by growing conditions, type of fermentation, and factors inherent to the processes (for example, increase in temperature and aeration). Therefore, it is necessary to carry out further research focusing not only on expanding the production scale of these compounds but also on developing new technologies or even on adapting existing ones, which make it possible to demonstrate the high potential of these metabolites. One of these cases is membrane emulsification, which allows the production of emulsions with greater kinetic stability, malleability, spreadability, penetration, and bioavailability. Associated with this, the emulsification of the membrane can prolong the storage period of the bioproducts.

One of the crucial challenges is to understand the mode of application that allows satisfactory distribution of the biocontrol agents at the target weed to enhance efficiency and decrease the cost of treatment. Second, there are hurdles in developing effective technology for commercial mass production. However, the *Phoma* spp. can be easily grown in artificial media, and thus, the economically affordable product can be developed. The efficiency of mycoherbicides depends upon the interaction of temperature and moisture, sensitivity to UV light, and desiccation (El-Sayed 2005). The accurate formulation is considered as the main factor to increase both efficiencies of application and biocontrol agents (Evans and Reeder 2001). Appropriate formulations need to be used to improve product stability, bioactivity, and delivery as well as to integrate the mycopesticide into a pest management system (Charudattan 2001).

All the above-mentioned factors should be taken into account in developing a prosperous mycoherbicide from *Phoma* spp. for the efficient control of weeds, which implies the necessity of continuous attempts undertaken by researchers to verify their capability as the alternative for weed management.

Conclusions

To sum up, this review intends to provide insights into *Phoma sensu lato* having remarkable mycoherbicidal efficacy, aiming at the replacement of synthetic herbicides and looking for strategies that are less aggressive to the environment in the future for weed control.

The biomolecules produced by *Phoma* spp. are promising for the development of natural products such as bioherbicides. Biological control is a natural way of weed control leading to the development of sustainable agriculture. In recent years, there has been a gradual increase of interest among researchers related to the selection of biological agents, development of technology for the production of biologically active metabolites, and efficiency tests on a laboratory scale, in addition to purification, concentration, and formulation of bioproducts. However, there are still many challenges, due to the low productivity of secondary metabolites that is influenced by the conditions of the culture medium, type of fermentation, and factors inherent to this, with changes in temperature and aeration during the process. Because of this, it is necessary to develop more research, focusing not only on increasing the scale to produce these compounds but also on developing or even adapting existing technologies that allow greater expression of the potential of these compounds.

Author contribution MR conceived and designed the review. ZB contributed substantially. SS and MVT co-wrote the manuscript. MR critically revised the mss. All authors read and approved the manuscript.

Declarations

Ethical statement This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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