REVIEW ARTICLE

The Foliar Fungal Pathogenic Metabolites as Promising Alternatives to Chemical Herbicides: Recent Developments, Future Perspective and Commercialization

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Abstract

Weeds harbour wide variety of microorganisms having beneficial, neutral and phytopathogenic effects. Weed microbiome discoveries could fuel progress in sustainable agriculture, such as the development of microbial herbicide products. Weed infecting phytopathogenic living fungal cells (mycelia or spores) and their natural products have been studied as producers of mycoherbicides. The application of biological and biochemical (natural or biorational) herbicides based on specific weed pathogens and natural products, respectively, is believed to assist the decreasing harmful impact of the chemicals. Cell free broth of several plant pathogenic fungi have been enthusiastically investigated for substitutes of synthetic agrochemicals against weeds. However, all such studies conducted on pure compound with high purity which have limitations due to high costs. It was found that herbicide in cell-free culture broth of fungi were largely composed of various nature of different metabolites with the ratio varying with culture time. Crude broth in a form of cell-free culture broth showed high herbicidal activity against weeds. So, cell-free culture broth as a crude product could be serve as a potential cost-effective and environmental-friendly herbicide in agriculture. The application of mycometabolites in agricultural weed management are safer to the user and the environment. They were formulated and applied in the same manner as chemical herbicides. This review aims at summarizing the studies on the application of mycometabolites as a lucrative, novel source of secondary herbicidal compounds for management of weeds. More effort should be expended in this area of research in the future, despite the obstacles that exist.

Keywords: Biorational, Development, Discovery, Foliar fungal pathogens, Fungal metabolites, Fungal spores, Mycoherbicides, Weed pathogenic fungi.

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Introduction

The management of weeds in current agriculture practices has been mostly dependent on chemical herbicides because almost no new herbicides mode of actions has been explored. The application of chemical control has aided humanity to increase crop productivity for many years, but over the past few decades the intensive use of synthetic herbicides has led to non-targeted adverse environmental effects, soil and water contamination and herbicide resistance in weeds. Considering this scenario, the prospection and discovery of new microbial-molecules appear as an important tool for the control of resistant weeds.

Various fungi with herbicidal potential have been discovered but very few have become commercial realities or viable alternatives due to biological, technological and commercial constraints. Herbicidal metabolites produced by fungi play an important role in host pathogen interactions and better alternatives for chemical herbicides mycoherbicide constraint. Some studies have shown promising results in the weed control using fermented broth containing the secondary metabolites produced by fungi via submerged fermentation. Secondary metabolites can damage weeds by penetrating the plant followed by the destruction of the cell wall and induction of necrotic lesions. The mycoherbicides and Fungal derived natural product herbicides (FDNPH) are considered as relatively safe alternatives for weed control in both organic and conventional agriculture.

Mycoherbicides developed from fungal phytotoxins have been used for controlling weeds. It has been considered that mycoherbicides can be better supplementary tools in weed control. In pursuit of a better environmental sustainability, industries are now moving away from the conventional and chemically manufactured compounds and are focusing on development of biobased naturally harvestable compounds to reduced carbon footprints, ecological and environmental impacts as well as to reduce manufacturing costs. It can be achieved by harnessing the versatile potential of weed inhabiting/infecting fungi. Fungi known as important microorganisms for industrialization. Many fungal secondary metabolites that include wall degrading proteins, toxins, antibiotics, vitamins, amino acids and organic acids have been discovered, leading to

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a productive growth of bio-commercialization. These metabolites consist of a wide array of chemical structures. They can be key factors of pathogenicity or virulence, can have different behaviors with respect to the host varying from strictly host-specific to completely non-specific compounds, and can act with different mechanisms affecting several sites in the host. Mycoherbicides developed from fungal phytotoxins have been used for controlling weeds. It has been considered that mycoherbicides can be better supplementary tools in weed control. In pursuit of a better environmental sustainability, industries are now moving away from the conventional and chemically manufactured compounds and are focusing on development of biobased naturally harvestable compounds to reduced carbon footprints, ecological and environmental impacts as well as to reduce manufacturing costs. It can be achieved by harnessing the versatile potential of weed inhabiting/infecting fungi. Fungi known as important microorganisms for industrialization. Many fungal secondary metabolites that include wall degrading proteins, toxins, antibiotics, vitamins, amino acids and organic acids have been discovered, leading to a productive growth of bio-commercialization. These metabolites consist of a wide array of chemical structures. They can be key factors of pathogenicity or virulence, can have different behaviors with respect to the host varying from strictly host-specific to completely non-specific compounds, and can act with different mechanisms affecting several sites in the host. The exploitation of mycometabolites in agricultural weed management are safer to the for user and the environment. They have formulated and applied in the same similar manner as chemical herbicides. Plant pathogenic fungi that are classified as necrotrophs, hemibiotrophs and biotrophs constitute one of the main infectious agents in weeds, causing alterations during developmental and later stages, taking nutrients from the plants they invade and therefore resulting in huge damages to plants. Fungi infect weeds using different strategies: biotrophs exploit plants' resources, whilst keeping the host alive; necrotrophs kill the host in order to thrive off dead or dying tissue; and hemibiotrophs have an asymptomatic phase followed by a necrotrophic stage (Horbach *et al.*, 2011).

This paper reviews on the recent developments, future prospective and commercialization of biochemical (natural or biorational) herbicides based on specific fungal weed pathogens. and it believe to assist the decreasing harmful impact of the chemicals.

FUNGAL METABOLITES AS NATURAL HERBICIDES

Diversity of fungi constitutes the most extraordinary reservoir of life in the biosphere that we have only just begun to explore and understand. Out of 69000 species and genera of fungi recognized only very meager number of species has been evaluated for their mycoherbicidal potential. Most of the mycoherbicide candidates tested belong to Deuteromycetes, a large and varied class of conidial non-sporulating fungi. Species of Colletotrichum, Alternaria, Septoria, Phompsis, Phoma, Phaeoseptoria, Ascochytaetc are the major genera developed as mycoherbicides.

There are many Mycoherbicides routinely used in well developed countries such as UK, USA, Canada etc (Table 1). They have been developed from indigenous fungi that occur naturally at endemic levels and are as effective or more effective than chemical herbicides on their specific weed host.

The idea of using plant pathogens to control weeds is almost as old as the science of plant pathology itself. The search for natural products with novel herbicidal activities is of great importance for agriculture, since most existing herbicides are either banned or inefficient due to resistant weeds, and the flow of novel herbicides identified by classical chemical screening is dramatically reduced. Theoretically all the classes of plant pathogens have herbicidal potential, but fungi appear most promising due to their strong mechanism of action. They can enter the host without the assistance of vector. Fungi that are virulent, host specific and genetically stable but constrained naturally by low inoculums production, environmental constraints and poor dissemination. So fungal metabolites are probably the best candidate for exploitation in weed management systems. Biorational approach is the use of toxic secondary metabolites of fungi which are considered to be safest pesticides for the environment and people. For example, they pose minimal to no risk to the environment due to their chemical make-up, rapid degradation or the small amounts required for effective control. Both pathogenic as well as non-pathogenic fungi are known to synthesize array of phytotoxic metabolites mentioned in Table 2.

The rationale behind this approach is the use of toxic secondary metabolites of fungi or phytotoxins, which are the safest pesticides for the environment and people. Phytotoxins are usually isolated from in vitro cultures of the pathogen grown on either solid or liquid media (Strange, 2007). Phytotoxins are largely represented by low molecular weight secondary metabolites capable of deranging the vital activity of plant cells or causing their death at low concentration. The effect of phytotoxins on plants is characterized by the appearance of specific symptoms, wilting and general growth suppression as well as chlorosis, necrosis and spotting of aerial portions are the most common. The weed pathogenic fungi are grown in a suitable media for a particular incubation time to extract herbicidal compounds (Banowetz *et al.*, 2008). It has become increasingly evident that phytotoxins are important disease determinants. Various approaches has have been developed made to improve the amount and quality of phytotoxins which is synthesized by fungal bio-control agents (Dayan *et al.,*2000). Most of the information available on the phytotoxicity of fungal products is not useful in evaluating their potential as herbicides. In the few cases in which a molecular target site has been established, it has generally been one that has not yet been exploited by the herbicide industry (Duke *et al.,* 1996). Some fungal phytotoxins also vary in host specificity, ranging from host specificity to having no specificity whatever (Strobel *et al.,* 1992). The phytotoxins Tentoxin (a cyclic tetrapeptide) which is produced by several Alternaria species and causes severe chlorosis in many of the problem species associated with soybeans and maize without affecting either crop (Duke and Lydon 1987). Non-host specific toxins are of considerably more interest because they often have the potential for killing a range of weeds without phytotoxicity to crops (Duke *et al.,* 1991). It is certain that biodegradable, microbially derived herbicides will be on the market within the next decade (Duke *et al.,* 2000). Indeed, the phytotoxins produced by weed pathogenic fungi are an efficient tool to design natural safe

Table 1: Fungal spores developed/under development as a biocontrol agent.

Weed	*Pathogen*	*Status*
Abutilon theophrasti	*Colletotrichum coccodes* (Wallr.) Hughes(Velgo)	F
	Fusarium lateritium	D
Aeschynomene virginica L.	*Colletotrichum gloeosporioides f sp. aeschynomene* (CollegoR)	F
Albizzia julibrissin	*Fusarium oxysporum* f sp *perniciosum*	E
Ambrosia trifida	*Fusarium lateritium*	C
Annoda cristata L Schlecht	*Alternaria macrospora Zimm*	C
	Fusarium lateritium	D
Cannabis sativa	*Fusarium oxysporum f sp cannabis*	D
Cassia occidentalis L	*Alternaria cassiae* Jurair & Khan (CasstR)	F
Chondrilla juncea L	*Puccinia chondrillina* Bub & Synd	F
Cirsium arvense	*Fusarium roseum*	C
Crotolaria spectabilis	*Fusarium udam f sp crotolariae*	D
Cucurbita texana	*Fusarium solani f sp cucurbitae* Synd & Hans.	D
Cuscuta chinensis L.C.	*Colletotrichum gloeosporioide f sp cuscutae* (LuboaR)	F
Lupiniformis kroch	*Fusarium tricinctum*	D
	Alternaria cuscutacidae Rudak	F
Hydrilla verticilliata	*Fusarium roseum*	D
	Fusarium solani	D
Malva pusilla	*Colletotrichum gloeosporioide f sp malvae* (BiomalR)	E
Morrenia odorata	*Phytophtora palmivora(smith) Leonian* (DevineR)	F
Orobanche spp.	*Fusarium oxysporum var orthoceras*	F
Parthenium hysterophorus L	*Alternaria tenuis* Auct	A
	A. zinniae Pape	A
	A. alternata (Fr.) Keisler	B
	A. dianthii Steyens & Hall	B
	A. macrospora Zimm	B
	Curvularia lunata (Walk) Boed	B
	C. senegalensis (Speg) Sub	B
	Colletotrichum gloeosporioides (Penz) Sacc	B
	C. Capsici (Syd) Butler	B
	Cladosporium cladosporioides Fr Nar	B
	Cercospora parthenii Syd	B
	Dreschslera indica (Rai et al) Mouch	B
	Fusarium equiseti (Corda) Sacc	B
	Fusarium oxysporum Schl ex Fr	B
	Myrothecium roridum Tode ex Fr	B
	Phoma herbarum West	B
	Puccinia abrupta f sp parthenicola	C
	P. melampodii Diet & Howlay	A
	Sclerotium rolfsii Sacc	B
	Bremia lactucae Regel	A
	Erysiphae cichoracearum De ex Merat	A
	Cercospora partheniicola Chupp & Greene	A
	Sphaerotheca fuliginae (Schl) Pollcci	A
Rumex cripspus L.	*Uromyces Rumicis (Schum)* Wint	C
Sida spinosa	*Colletotrichum malvarum* (Braun & Casp) South	C
	Fusarium lateritium Nees ex Fr	C
Xanthium strumarium L. *X. spinosum* L	*Colletotrichum orbiculare* (Berk. & Mont.) V. Arx	F

Sources: Charudattan (1990)

A = Discovered B = Pathogenicity confirmed
C = Safety test confirmed, Green house evaluation in progress D = Under small scale field test
E = Under large field tests comparable to commercial evaluation F = Commercialized G = Status unknown

Table 2: Phytotoxic Metabolites with Promising Herbicidal Properties

S.No	*Fungal Source*	*Phytotoxin*
1	*Alternaria alternata*	Maculosin
2	*Alternaria alternata*	Tentoxin*
3	*Alternaria alternata*	AAL- toxin*
4	*Alternaria alternata*	Tenuazonic acid
5	*Alternaria eichhorniae*	Peryleneginones, Alteichin
6	*Alternaria kikuchinana*	AK- Toxin
7	*Alternaria mali*	AM -Toxin
8	*Alternaria porri*	Porrolide*
9	*Alternaria helianthi*	Radicinin
10	*Alternaria zinnia*	Zinniol
11	*Bipolaris cynodonti; Phoma distruciva;Phoma exigua;Penicillium roqueforti*	Ermophilans
12	*Cercospora kikuchi*	Cercosporin
13	*Fusarium moniliforme*	Moniliformin*
14.	*Fusarium* sp.	Fusaric acid*
15.	*Fusicocuma mygdale*	Fusicocin
16.	*Colletotrichum tabacum; C. nicotianae*	Colletotrichin
17.	*Rhizoctonia solani*	Gliotoxin
18.	*Ascochytahyalo spora*	Aschochytine, Pyrenolide-A, Hyalopyrone
19.	*A. cypricola*	Cyperine
20.	*Dreschlera maydis; Dreschlera oryzae, Dreschlera sorghicola*	OphiobilinsI, A, C. Epihydroophiobolin A, 6-Epiophiobolin
21.	*Dreschlera sorokiana, Bipolaris sp.*	Perhelminthosporol
22.	*Dreschlera indica*	Curvulins
23.	*Dreschlera nodulosum*	Tryptophol
24.	*Peacilomyces variotii*	Cornexistin
25.	*Gliocladium virens*	Viridiol
26.	*Penicillium charlesii*	Citreoviridin
27.	*Helminthosporium carbonum*	HC- Toxin
28.	*Streptoverticillium* sp	Cyclocarbamide A, B
29.	*Cochliobolus spicifer*	Spiciferones A, B, C
30	*Chaetomium globosumi*	Chaetoglobosins
31	*Aspergillus ustus*	Dihydropergillin
32	*Aspergillus niger, Aspergillus glaucus*	Nigerazine A, B
33	*Aspergillus niger*	Orlandin, Kotanin
34	*Aspergillus candidus*	Terphenyllin, Hydroxy terphenyllin
35	*Aspergillus terreus,*	Mevinolin, Acetylaranotin
36	*Cephalosporium recifei, A. flavus,*	Macrolides
37	*Chaetomium trilaterale*	Oosporein
38	*Myrothecium verrucaria; Myrothecium roridum*	Trichothecones

SOURCE: Pandey, 1999.

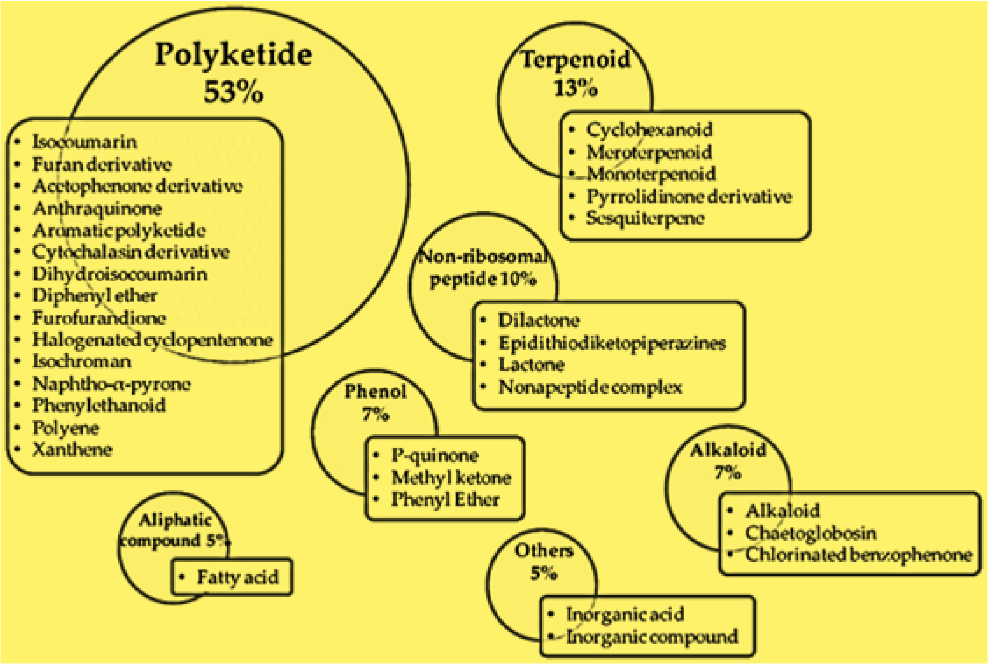

Fig. 1: Diagram of various categories of fungal metabolites and percentage of compounds in each category.
Source: Strange, 2017

mycoherbicides (Strange, 2007). Their use could avoid that of synthetic pesticides causing resistance in the host plants and long-term impact of residues in agricultural products with risk for human and animal health. The predominant chemical family within this category is isocoumarin, followed by furan derivative and acetophenone derivative. Twelve other chemical families are also represented within this group (Fig. 1). After polyketides, the categories, ordered according to the number of metabolites with herbicidal properties, are the following: terpenoids (13%), nonribosomal peptides (10%), phenols (7%), alkaloids (7%), aliphatic compounds (5%) and other compounds (5%) such as inorganic acids (Fig. 1).

Fig. 1. Graphical abstract of the different categories in which the fungal metabolites are included, indicating the percentage of compounds in each category.

Both pathogenic as well as non-pathogenic fungi are known to synthesize array of phytotoxic metabolites. Some of them have been evaluated, patented and few of them have been commercialized as herbicides. We have significantly tested herbicidal activity of partially purified filtrate (CFCF) of C. gloeosporioides f. sp. parthenii FGCC #18, C. dematium FGCC#20, F. oxysporum FGCC#39, F. solani FGCC#86, S. rolfsii FGCC#19, Aspergillus flavus FGCC#14 and Curvularia lunata FGCC#41 have been observed against Parthenium hysterophorus (Thapar *et al.,* 2002; Pandey *et al.*, 2003, 2004) and Lantana camara (Saxena and Pandey 2000; Pandey *et al.,* 2005; Singh 2007; Singh & Pandey 2019). Saxena and Pandey (2001) reported extremely high biological activity in CFCF of Alternaria alternata FGCC#25 against L. camara. Pandey *et al.,* 2007 reported extremely high biological activity in CFCF of Helminthosporium sp. FGCC#74 against Hyptis suaveolens. Singh 2007 reported herbicidal compounds from some selected fungi against different noxious weeds of Madhya Pradesh. Alternaria eichhorniae metabolites Perlenginones and Alteichin has shown good herbicidal potential agent against Water hyacinth weed.

Fungal Secondary Metabolites divided into four main chemical classes *viz.,* polyketides, terpenoids, shikimic acid derived compounds and non-ribosomal peptides. Whole genome analysis of fungi revealed that ascomycetes have more genes of secondary metabolism than archeo asocomycetes, basidiomycetes, chtridiomycetes and hemi ascomycetes and zygomycetes have no such genes nothing(Collemare *et al.*, 2008). Ascomycete genomes code for on average 16 polyketide synthases (PKS), 10 non-ribosomal protein synthases (NRPS), two tryptophan synthetases (TS)and two dimethylallyl tryptophan synthetases (DMATS) with crucial importance in SM synthesis. These types of SM genes encode signature enzymes that can be enriched in secondary metabolism gene clusters and responsible for main synthesis steps of metabolites. PKS–NRPSs have been identified only in ascomycetes, with an average of three genes per species. Whole-genomic analysis have identified 12–15 PKS genes in F. graminearum (Sieber *et al.*, 2014), where six have been linked to metabolites.

POTENTIAL IMPROVEMENTS

There are several improvements that researchers around the globe are currently attempting to overcome the current industrial limitations. Undergoing studies are being done especially based

on the idea of utilizing cheaper raw biomaterials as growth media or as an alternative carbon source, such as using sugar cane bagasse and molasses as substrates in solid state fermenters (Veana *et al.,* 2014) or using plant oil to replace glucose as carbon source (Darvishi *et al.*, 2009). Barig and colleagues are also extensively experimenting with various physicochemical parameters, such as culture viability under low pH, and minimized up-scaled sterile conditions (Barig *et al.,* 2011), to explore unique combinations of growth conditions that would optimize fungal growth and at the same time, limit or even hinder the unwelcome growth of contaminant organisms.

The application of fungal phytotoxic metabolite could be a replacement for synthetic herbicide which is more economical in controlling weeds than the synthetic herbicides. We are confident that the future of fungal metabolites-based herbicide will accelerate agriculture production and serve as an alternative to the chemical herbicides because of its safety in the environment.

Thus, the study of natural substances with herbicidal activity has great prospects. The known spectrum of the fungal species producing biologically active substances (BAS) of this type is yet very narrow. Therefore, the search for new BAS producers and the study of their properties are very topical. In order to attain the goal, set it is necessary to solve the following tasks:

- Search for phytopathogenic fungi of weeds from different ecological zones.
- Determination of the toxicity of the active strains of weed pathogenic fungi under laboratory conditions and the isolation of toxins responsible for biological activity.
- Physico-chemical characteristics of new fungal phytotoxic metabolites, the structure and mechanism of the action of purified substances.
- Scaling up production of fungal isolates with sufficient herbicidal activity and extraction of secondary metabolites for further testing.
- Testing of identified fungal secondary metabolites with herbicidal and insecticidal activity on agriculturally important crops.
- On the other hand, many promising biomolecules are early discarded during the stages of bioherbicide development because they present low herbicidal activity. In a general way, low efficiency is a consequence of the very low concentration of biomolecules in the fermentation media. Therefore, some strategies to increase the concentration of these molecules are essential to obtain an efficient product.
- The development of FDNPHs based on fungal phytotoxins is delayed because little is known about their selectivity and general toxicity. The poor selectivity of natural phytotoxins may limit their potential as plant protection products. The use of many fungal phytotoxins as natural herbicides is still limited because they cannot penetrate leaf cuticle without injury and a little is known on their selectivity. Most natural phytotoxins seem to be unable to penetrate the plant cuticle. In the case of chemical herbicides, the problem of their effective absorption into plant tissues is often solved by supplementation with the appropriate adjuvants (surfactants, penetrants, etc.). The effectiveness of the foliar-applied herbicides on target weeds is highly affected by the type of adjuvant added into formulation. It is necessary to use an adequate combination of adjuvants in the formulation to increase the herbicidal activity. Adjuvants are substances present in a formulation with the aim of modifying the biological activity or the application characteristics of the formulation. The adjuvants in formulations of chemical herbicides are used as wetting agents, penetrants, spreaders, co-solvents, stickers, emulsifiers and others. The practical selection of compatible adjuvant is a complicated task because their positive effect is highly dependent on many factors: the nature of the active ingredient, weed and crop features and application techniques. Our observation indicates importance of selection and use of adjuvants in order to increase the leaf penetration and herbicidal activity of natural compounds. Searching for the most appropriate adjuvant for phytotoxins, generally commercial products used varying in the type and the nature of hydrophilic and lipophilic segments in their molecules. Some non-ionic adjuvants like isodecyl alcohol ethoxylate, Tween-20 (polyoxyethylene sorbitol ester and ethyl and methyl esters of vegetable oil and one anionic adjuvant sodium lauryl sulphate were used in the formulation.
- The hydrophilic-lipophilic balance (HLB) is commonly used to suggest the applicability of surfactants (e.g., emulsifiers, detergents) as activator adjuvants. Formulations containing distilled water or culture filtrate and different adjuvants (palm, soybean or mineral oil and Tween® 80) were evaluated in order to increase the bioherbicidal activity through post-emergence bioassays. The herbicidal activity of culture filtrate was improved using different combinations of adjuvants. For instance, the herbicidal activity of tenuazonic acid in field experiments was enhanced and stabilized due to the addition of surfactant JN (fatty alcohol polyoxyethylene ether) and lipophilic penetrant laurocapram (1:3, v/v) (Zhou *et al.,* 2019; Qiang *et al.,* 2008)

FUTURE PROSPECTIVE

Fungal natural compounds present a great potential as natural herbicides. Todays research catering to the needs of future are driving modern agriculture towards crop production systems that are healthier, safer, and friendlier to the environment as consumers demand pesticide free products and environmentally safe cultural practices. Considering these perspectives, the richest sources of natural compounds present in nature and their ecology, assume higher and higher importance and can increase the possibility of finding natural herbicides with new scaffolds and modes of action, fundamental factors overcoming resistance in weeds to conventional, synthetic herbicides. Being the result of co-evolution of the producing organism and its biotic environment, these compounds can have high target selectivity, with potentially reduced risks for humans and non-target organisms. Furthermore, they can have a shorter environmental half-life than synthetic compounds, thus reducing potential environmental impact. We could see how important it is to research deeper into this metabolic treasure trove, to improve our industrial yield and bring benefits to the society as a whole, as well as reducing human's carbon footprints.

ECONOMICS FOR DEVELOPMENT OF MYCO HERBICIDES

Fungal metabolites-based herbicides have been regarded to be cost effective. Zormner *et al.* (1993) have estimated that development cost regarding mycoherbicide was about 1.5 to 2 million, which is much lower than that required for development of effective chemical herbicide formulation (about US $ 10-20 million). Bower (1982) estimated that the cost of application of Collego was about $ 29/ha.

COMMERCIALIZATION OF MYCOMETABOLITES AS HERBICIDE

Fungal metabolites, both primary and secondary, are a subset of a larger repertoire of natural compounds that act as intermediary in the interplay between fungi and the ecology, hence opening up a potential industrial avenue to explore. Indeed, mycological biotechnology, as it stands now, is an important and ever-growing economic driver as industries begin to realise the potential and the cost-effectiveness of bio-production, with around 40% of the total drugs approved for commercial market being of natural products or biologically modified natural metabolites. Nevertheless, the industry is not without its technical limitations. Several significant technical hindrances to successful cultivation and large-scale bio-production of useful microbial (including fungal) natural products include relatively high capital and subsequent cultivation cost, stringent need for sterile conditions, and expensive media components and carbon source. Barig and colleagues (Barig *et al.,* 2011) reported in 2011 that the main issue riddling most microbial fermentation plants is the stringent need for sterile conditions, as up-scaled, industrial fermenters are typically exposed to a working environment that could be extremely difficult to keep sterile, unlike the more manageable sterile conditions in the laboratory. Because of the nature of microbial cultures, especially when non-fastidious growth media are involved (for instance, glucose used as carbon source), undesirable growth of contaminating colonies from other microbial organisms within the fermentation tanks may jeopardize the output performance of the cultivated industrial strain of interest, and may reduce the quality of the metabolites that would be harvested and purified. Furthermore, high cultivation cost is directly proportional to the complexity of the media components needed for the cultivation process and is inversely proportional to the size of the market for the metabolic product being harvested – higher cost effectiveness could be associated with small, niche market for metabolic products of less economic demands, and vice versa. In addition to this, when a medium requires a large scale preparation, certain key ingredients such as glucose (carbon source) would become costly, leading to a reduced industrial cost-effectiveness (Barig *et al.*, 2011; Jamal *et al.,* 2008). It is reported that growth media components carry a strong impact on global industrial bioprocesses and can account for 30% of the total production cost (Mattanovich *et al.*, 2014).

CONCLUSIONS

Mycoherbicides based on Fungal metabolites for weed control is nowadays gaining momentum. New mycoherbicides will find a place in irrigated tropical, sub-tropical agro-ecosystems, forestry, waste lands as well as in managing parasite weeds or resistant weed control. Research on synergy test of pathogens and pesticides for inclusion in IPM, developmental technology, fungal toxins, application of biotechnology, especially genetic engineering, is required. In the search for alternative solutions to weed control, the interest in application of bioactive secondary metabolites has increased. The success of natural products or natural product derived products in weed management is weak compared to that of insecticide and fungicide. The biochemical or biorational herbicide available for organic farmers and those who wish to reduce synthetic herbicide use are ineffective and costly to use. In this review, we found that original culture filtrates were applied in the foliar spray bioassays, showed good results. It is likely that if these culture filtrates are used in a concentrated form, these will be more toxic to weed species.

The great structural diversity of fungal phytotoxins with high potency and unique mechanisms of action (compared to synthetic herbicides) make fungal toxins highly attractive for discovering herbicidal activity. Even if natural phytotoxins are not necessarily suitable for direct use as a commercial herbicide, the identification of mechanisms is very important for new herbicide developments. Newly developed herbicides with environmentally friendly component could be used more safely in integrated pest management systems. Further studies are required to isolate the active herbicidal constituents from these fungal culture filtrates. The problem of the development of ecologically safe pesticides with new mechanisms of action is very urgent. The main reasons for that are as follows: first, the appearance of weed forms resistant to permitted pesticides, second, the strict requirements to the weedicides applied in terms of their safety for people and the environment. That is why the attention of researchers has been increasingly attracted by a compromise option, the isolation and characterization of pathogenicity factors of biocontrol agents, mainly toxins, in order to create new pesticides on their chemical basis. For a successful research and development process leading to a commercial product, a wide range of criteria (biological, environmental, toxicological, regulatory, and commercial) must be satisfied from the beginning. Among the major challenges to be faced by the candidate products to reach the market are the sustainable use of raw materials, the standardization of chemically complex extracts, and the regulatory requirements and approval. The unique set of secondary metabolites produced by fungi may play an important role in weed management as new products directly, as novel chemical frameworks for synthesis and/or for identifying original modes of action. The tremendous promising herbicidal potential of many of these natural products reported for noxious weeds in this current review will prompt a continued interest in developing fungal metabolites as natural safe herbicides.

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