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Fungal Metabolites Based Cell Free Filtrates: A New Era of Eco-Conscious Natural Herbicide

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Weeds pose a major challenge to agriculture worldwide, and herbicides have long been the primary strategy to this problem. The widespread use of herbicides has triggered increased weed resistance, which often necessitates higher application concentrations. This, in turn, leads to greater environmental persistence, hindering the natural breakdown of these chemicals, it causes higher persistence in the environment, impeding natural environmental breakdown. Each year, nearly 3 billion kilograms of pesticides are applied worldwide, amounting to an estimated global expenditure of 40 billion USD. Herbicides accounted for the majority of imports at 54.51%, followed by insecticides at 21.71% and fungicides at 17.81%. While herbicides remain a critical component of modern agriculture, increasing concern about the extensive use of agrochemicals and their effects on human health has emerged as a major public health challenge. As a result, numerous countries have implemented regulatory policies to restrict or ban certain herbicides, such as paraquat and glyphosate. Due to its high toxicity and documented links to suicide, this herbicide has been banned in over 50 countries worldwide. As a result, there has been growing interest in environmentally sustainable alternatives, such as microbial bioherbicides. Despite their potential, bioherbicides continue to face challenges in efficacy, as reflected by their limited adoption in commercial and industrial applications.

Fungi constitute a valuable biological resource that can be harnessed as biotechnological agents for effective weed management. Interestingly, current research shows a greater focus on potential or commercial bioherbicide products derived from fungi compared to those developed from bacteria. Fungi associated with plants may have both advantageous and harmful impacts. Among the approximately 150,000 known fungal species, nearly 8,000 are classified as phytopathogens. Key strategy fungi employ to initiate plant infection involves producing enzymes that break down the plant cell wall. These enzymes catalyze the hydrolysis of cell wall polysaccharides, promoting fungal colonization and enabling the uptake of nutrients vital for metabolic development. In addition, fungi utilize specialized mechanisms, such as the synthesis of mycotoxins and hormones, that contribute to a more selective antagonistic profile, an essential characteristic in the development of effective bioherbicides. Harnessing plant-pathogenic fungi and their metabolites for biological weed control presents promising avenues for future innovation and sustainable agricultural practices. The use of viable fungal cells or their natural metabolites offers an environmentally friendly approach to effectively managing weed populations. This approach is eco-friendly and avoids herbicide resistance. As organic horticulture continues to gain importance, the demand for innovative mycoherbicides to manage weed growth has risen substantially. Potential mycoherbicides can be formulated from fungal pathogens, naturally occurring compounds, and extracts derived from organic materials. During my PhD research, over 500 fungal isolates pathogenic to major weeds of Central India, including Parthenium hysterophorus, Lantana camara, Xanthium strumarium, Hyptis suaveolens, Chromolaena odorata, Antigonon leptopus, and Sida acuta, were successfully recovered. These include several fungal species, notably Colletotrichum gloeosporioides f.sp. parthenii, C. dematium, Myrothecium roridum, Sclerotium rolfsii, Fusarium solani, F. oxysporum, Alternaria alternata, A. macrospora which have demonstrated notable pathogenic capabilities and satisfied most of the requirements desired for mycoherbicidal development for above mentioned weeds [1].

The concept of employing fungal spores for weed control dates back to the very origins of plant pathology as a scientific discipline. Fungi that exhibit high virulence, strict host specificity, and genetic stability, despite being naturally limited by low inoculum production, environmental dependency, and inefficient dissemination, represent some of the most promising candidates for use in weed management systems [2]. To address the limitations of mycoherbicides, utilizing natural herbicidal compounds extracted from fungal culture filtrates emerges as an effective alternative strategy for weed management. Fungal phytotoxins are naturally occurring secondary metabolites synthesized by plant-pathogenic fungi during interactions with their host organisms. The potential use of fungal toxins as herbicidal agents has been extensively reviewed across numerous scientific publications [3-14]. Fungal toxins belong to a diverse array of naturally occurring compound classes, including aromatics, amino acids, coumarins, isocoumarins, cytochalasans, ethanones, furopyrans, nonenolides, oxazatricycloalkalenones, pyrones, spirophytotoxins, terpenes, trichothecenes, and other complex molecules characterized by unique carbon skeleton [15].

Below is a detailed table 1 categorizing fungal phytotoxins by chemical structure type, along with notes on their biological activity and herbicidal potential.

Table 1: Fungal Toxin with Chemical Structure Type, Biological Activity and Herbicidal potential.

Compound Class	Chemical Structure Type	Biological Activity	Herbicidal Potential
Aromatics	Benzene ring systems with functional groups	Inhibits photosynthesis and respiration	Can selectively suppress broadleaf weeds
Amino Acids	Simple to modified amino acid derivatives	Involved in metabolic interference	Can mimic or block plant signaling pathways
Coumarins & Isocoumarins	Fused lactone-benzene structures	Disrupts cell division and auxin transport	Effective against fast-growing invasive species
Cytochalasans	Macrocyclic lactones with polyketide features	Binds to actin filaments, disrupting cytoskeleton	Target-specific weed inhibition
Ethanones	Small ketone molecules with alkyl/aromatic groups	Alters membrane integrity	Moderate phytotoxicity, suitable for mixed formulations
Furopyrans	Fused furan-pyran ring systems	Affects photosynthesis and chlorophyll degradation	Promising for foliar application
Nonenolides	Nine-membered lactone rings	Inhibits seed germination	Potential for pre-emergent herbicidal use
Oxazatricycloalkalenones	Complex heterocyclic rings with nitrogen and oxygen atoms	Multimodal enzymatic inhibition	Highly potent, though production is often a challenge
Pyrones	Six-membered lactones derived from pyran	Disrupts cellular metabolism	Useful in post-emergent weed control
Spirophytotoxins	Spiro-connected ring systems	Targets hormonal regulation in plants	Promising for selective and systemic action
Terpenes	Isoprene-derived hydrocarbon skeletons	Alters plant hormone balance and cell wall synthesis	Widely studied; strong candidates for biocompatible herbicides
Trichothecenes	Epoxidized sesquiterpenes	Inhibits protein synthesis in plant cells	Highly effective but requires safety considerations
Others (Complex Skeletons)	Unclassified unique carbon frameworks	Varies depending on structure	May offer novel modes of action for weed suppression

These fungal toxins, due to their diverse chemistry and targeted bioactivity, provide a rich source of scaffolds for herbicide development. Their specificity can reduce collateral damage to non-target species and minimize environmental impact compared to synthetic herbicides. However, challenges such as large-scale production, stability under field conditions, and regulatory approvals must be addressed. Incorporating these metabolites into integrated weed management systems or formulating them alongside bio-enhancers could improve their commercial viability.

The secondary metabolites represent a promising reservoir of novel chemical structures with distinctive modes of action, which can be harnessed either directly or through their derivatives as commercial herbicides [18]. Several fungal phytotoxins, such as Tentoxin (Alternaria tenusis) for Galium aparine, Cornexistin, AAL-toxins (Alternaria alternata) for Lemna pausicostata, Fumonisin (Fusarium moniliforme) for Duckweed (Lemna minor), Moniliformin (Fusarium oxysporum) for Jimsonweed, 5-Methyl-Trp (Cantharellus cibarius) for Water hyacinth (Eichhornia crassipes), Cinnacidin (Nectria sp.) for Amaranthus retroflexus, Cyperin (Arabidophsis thaliana) for Presussia fleischhakii and Maculosin(Alternaria alternata) for Spotted Knapweed (Centaurea maculosa) etc. have been successfully exploited [16,17]. Among the numerous microbial strains and their metabolites investigated, only a limited number of fungal species have been successfully commercialized and marketed under various trade names. Numerous non-pathogenic fungal strains have emerged as highly accessible sources of novel bioactive by-products. While considerable research has focused on the chemical characterization of various fungal metabolites, relatively limited attention has been devoted to assessing their herbicidal potential. Scientists should focus on discovering additional promising agents and developing rapid, efficient methods for their evaluation, production, and formulation. Technological advancements and the emergence of innovative techniques have significantly enhanced the efficiency and scope of biological herbicide applications for weed control.

Numerous naturally occurring phytotoxins exhibit distinct modes of action that set them apart from conventional herbicides, making them valuable tools for sustainable weed management. This makes them particularly valuable in tackling herbicide-resistant weed species and developing sustainable control strategies. For instance, tentoxin, a cyclic tetrapeptide produced by Alternaria spp., disrupts chloroplast development in germinating seedlings, causing chlorosis in susceptible plants. Similarly, trichothecenes, a class of sesquiterpenes with epoxide rings, inhibit protein synthesis by targeting ribosomal function, offering a potent mechanism against herbicide-resistant weed species. Cercosporin, a photosensitizing perylenequinone produced by Cercospora spp., generates reactive oxygen species upon exposure to light, leading to cell membrane damage in target plants. These unique biochemical pathways not only reduce the risk of cross-resistance with existing herbicides but also support the development of ecologically compatible bioherbicidal formulations. The rising demand for novel biochemical herbicides tailored for organic farming, alongside the pursuit of herbicides with innovative modes of action for conventional agriculture, continues to drive intensified research into natural products, either as direct herbicidal agents or as templates for the design of synthetic herbicides. A successful research and development pathway culminating in a commercial product requires early consideration and fulfillment of a broad spectrum of criteria, including biological efficacy, environmental safety, toxicological assessment, regulatory compliance, and commercial viability. Key challenges confronting candidate products en route to commercialization include ensuring the sustainable sourcing of raw materials, standardizing chemically complex extracts, navigating regulatory frameworks, and securing market approval.

The unique array of secondary metabolites synthesized by fungi presents a rich and underexplored resource for advancing weed management strategies. These compounds may be applied directly as bioherbicides, offering eco-friendly alternatives to synthetic chemicals. In addition, many of these metabolites serve as novel chemical frameworks for the design of new synthetic herbicides, enabling the development of compounds with enhanced selectivity and environmental compatibility. Importantly, their diverse mechanisms of action, ranging from inhibition of photosynthesis and protein synthesis to disruption of hormone regulation and cell structure integrity, introduce fresh avenues for tackling herbicide-resistant weed populations. Harnessing these metabolites, whether through direct application, chemical modification, or molecular modeling, could revolutionize both organic and conventional agricultural practices while contributing to sustainable pest control paradigms. The use of fungal phytotoxic metabolites offers a promising alternative to synthetic herbicides, potentially providing a more cost-effective and environmentally sustainable solution for weed control. I am confident that fungal metabolite-based herbicides will play a pivotal role in enhancing agricultural productivity while providing a safer and more sustainable alternative to conventional chemical herbicides. The remarkable structural diversity and encouraging herbicidal efficacy of numerous natural products highlighted in this editorial are likely to stimulate sustained interest in the development of fungal metabolites as safe, environmentally friendly herbicides.

Consequently, it is imperative for the research community to remain attuned to emerging innovations that foster more efficient extraction, analysis, production, and formulation of fungal metabolites for weed management. Advances in high-throughput metabolomic profiling allow researchers to swiftly identify bioactive compounds with herbicidal potential. Coupled with techniques such as mass spectrometry, NMR spectroscopy, and molecular docking, scientists can elucidate structural and functional properties of these metabolites with unprecedented precision. Moreover, improvements in fermentation technologies and bioreactor design have enabled scalable production of metabolites from non-pathogenic fungal strains, while novel formulation strategies, such as microencapsulation and nanoemulsions, enhance their field stability and targeted delivery. Together, these tools lay the groundwork for translating lab-based discoveries into viable agricultural solutions that are both ecologically sound and commercially feasible.

Advancements spanning the entire development pipeline, from fungal strain selection and genetic optimization to final product formulation and application techniques, are driving a new era of innovation in bioherbicide technology. These integrated breakthroughs are lowering production costs, improving product efficacy, and enabling scalable, field-ready solutions that can reach a wider range of agricultural systems. By addressing a major agronomic challenge, weed management, and reducing the dependency on synthetic chemical herbicides, fungal metabolites offer an environmentally safer and economically viable alternative. Their widespread implementation could not only enhance crop yields and soil health but also mitigate significant financial losses caused by invasive weed species, ultimately contributing to more sustainable and resilient agricultural practices. So, I want to conclude with a quote that Nature provides the blueprint, our role is to decode, refine, and apply it responsibly.

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