Fungal Seconadary Metabolites As Herbicides And Antibiotics

Sadaf Kalam
Department of Biochemistry
St Ann's College for Women,
Mehdipatnam, Hyderabad

A M Sylaja
Department of Biochemistry
St Ann's College for Women,
Mehdipatnam, Hyderabad

I. Introduction

Fungi encompass the largest biotic community after insects with its number exceeding 27,000 species (Sarbhoy et al., 1992).They colonize, multiply and survive in diversified habitats, *viz*. water, soil, air, litter, dung, foam, etc. Being ubiquitous and cosmopolitan in distribution they occupy all niches ranging from tropics to poles and mountain tops to the deep oceans (Hawksworth, 1991). The kingdom of fungi contains 1.5 million fungal species, of which 74,000 species are named. Several of the described species are known only as dead herbarium material while a mere 5% of species are isolated and available as pure cultures (Manoharachary et al., 2005). They are important sources of biotechnological products being used in many industrial fermentation processes, such as the production of enzymes, vitamins, pigments, lipids, glycolipids, polysaccharides and polyhydric alcohols (Adrio and Demain, 2003). During the past few decades, major advancements in medicine have arisen from lower organisms such as molds, yeasts and the other diver's fungi. Fungi are extremely useful in making high value products like mycoproteins and act as plant growth promoters and disease suppressors. Fungal secondary metabolites find their wide applications in agriculture, health and nutrition and have tremendous economic impact. In addition to this, fungi are extremely useful in carrying out biotransformation processes. Recombinant DNA technology, which includes yeasts and other fungi as hosts, has markedly increased market for microbial enzymes. Today, fungal biotechnology occupies a major position in the global industry due to its immense potential**.**

This template, modified in MS Word 2007 and saved as a "Word 97-2003 Document" for the PC, provides authors with most of the formatting specifications needed for preparing electronic versions of their papers. All standard paper components have been specified for three reasons: (1) ease of use when formatting individual papers, (2) automatic compliance to electronic requirements that facilitate the concurrent or later production of electronic products, and (3) conformity of style throughout a conference proceedings. Margins, column widths, line spacing, and type styles are built-in; examples of the type styles are provided throughout this document and are identified in italic type, within parentheses, following the example. Some components, such as multi-leveled equations, graphics, and tables are not prescribed, although the various table text styles are provided. The formatter will need to create these components, incorporating the applicable criteria that follow.

II. Fungal secondary metabolites

Natural product chemistry envelopes the study of an arsenal of compounds secreted by living organisms. Fungi are rich sources of thousands of secondary metabolites, which are low-molecular weight compounds (the number of the described compounds exceeds 100,000) being usually regarded as non essential for life and whose roles are quite versatile (Perez-Nadales et al., 2014). Secondary metabolites are widely defined as those organic compounds which are not directly involved in primary metabolic processes such as cell growth, cell division, cell respiration or photosynthesis (Keller et al., 2005). They are also derived from a few common biosynthetic pathways which branch off from the primary metabolic pathways and are often produced as families of related compounds, often specific for a group of organisms (Dewick, 2009; Hartmann, 2007).

A plethora of secondary metabolites (SMs) are produced by Fungi whose complexity and diversity is sometimes surprising. Fungal secondary metabolites have been of interest for humans for thousands of years. Fungal SMs can be categorized into four main chemical classes: polyketides, terpenoids, shikimic acid derived compounds, and non-ribosomal peptides. In addition to these, hybrid metabolites composed of moieties from different classes also occur, as in the meroterpenoids, which are fusions between terpenes and polyketides (Pusztahelyi et al., 2015).

III. Fungal metabolites as herbicides

Weeds cause enormous losses in crop yields both in quantity and quality besides they create health and aesthetic problems (Oerke,2006; Gadermaier et al., 2014; Kuester et al., 2014). A vast number of physical and chemical strategies have been employed to combat these natural hazards. Incessant use of synthetic agrochemicals to control weeds and to meet the burgeoning food demands has led to grave environment and health hazards (Waggoner et al., 2013; Gaba et al., 2017). These pose risk to non-target organisms including humans leading to societal and scientific concern agrichemicals exhibit residual toxicity resulting in high incidences of various types of cancers, hormonal and immunological disorders and allergies apart from their ill effects on reproductive system (Pandey 1998; Pandey et al., 2003). Since the xenobiotics are accompanied with several toxic effects, nowadays more emphasis has been focused on suppression of weed population to subeconomic and sublethal levels rather than their complete eradication (Saxena and Pandey, 2001). More initiatives are being taken towards the use of non-hazardous, ecofriendly and innovative alternatives. Thus, there is an enormous potential for screening of new secondary metabolites with applications in agrochemical and pharmaceutical industry.

Biological control proves to be the only cost-effective, environmentally benign and ecologically viable method available for the control of deadly weeds (Muller-Scharer et al., 2000). Weeds impose deleterious economic effects on humans and livestock. Microbial products tend to offer a non-chemical alternative in controlling noxious, invasive and pernicious weeds. Microbial secondary metabolites or agribiologicals are biotechnological products, which have provided new incentives for natural herbicidal products research. They are environmentally and toxicologically benign in comparison to traditional chemical herbicides.

Plant pathogens have long been considered to produce toxic substances that play a major role in pathogenesis. Phytotoxicity of secondary metabolites of plant pathogens is well known. Phytotoxins are defined as microbial metabolites that are harmful to plants at very low concentrations (Hoagland, 1999; Vikrant et al., 2006). Most of the plant pathogenic fungi produce toxins *in vitro* cultures and on *in vivo* host. Phytotoxins avoid the environmental problems as encountered by use of chemicals. Extensive survey of literatures on phytotoxic metabolites clearly indicates that extensive work has been done on the role of toxins involved in diseases of economically important crops and on weeds (Harding and Raizada 2015). The secondary metabolites appear to be a lucrative source of novel structures having unique mode of action which could be exploited as commercial herbicides directly or as their derivatives (Abbas et al., 1992; Quereshi et al., 2011; Duke, 2012). Several microbial products viz., Bialaphos, Gulfosinate, Tentoxin, Cornexistin, AAL-toxins, Fumonisin, Moniliformin, Macrocidins etc have been successfully exploited for the management of many weeds (Hoagland, 2001; Barbosa et al., 2002;Mo et al., 2014).

Among the microorganisms, since fungi are the most common pathogens of plants and therefore for weeds, the use of phytopathogenic fungi in biological control of weeds may represent a promising alternative to the use of chemicals or in Integrated Weed Management Systems (IWMS) (Hasan and Ayres, 1990). An effective approach to weed biocontrol is the use of toxic metabolites produced by weed pathogens, in addition or in alternative to the pathogen, or in integrated weed control programs. The replacement or the integration of traditional chemical control methods to plant disease by the use of microorganisms and/or their bioactive metabolites reduces the environmental impact of agricultural productions and gives efforts to the agricultural biological production which is more and more present in the national and international markets (Dayan et al., 2009). These bioactive secondary metabolites could play an interesting role in the induction of disease symptoms (phytotoxins) or of defence response (elicitors).

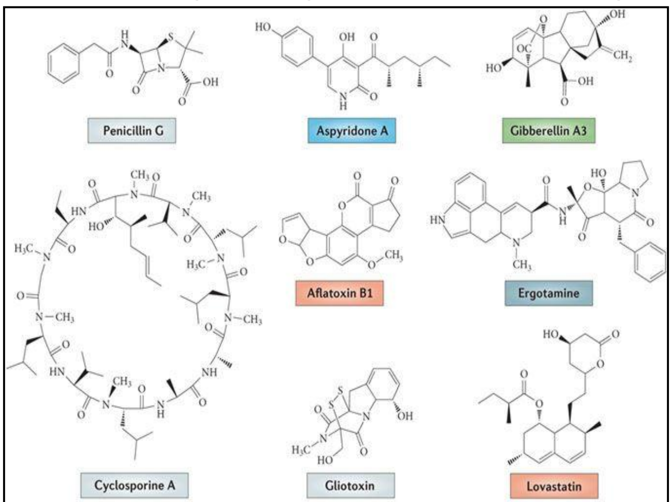
New herbicides with novel mode and mechanism of action have evolved great interest due to the rapidly evolving resistance to current herbicides (Cantrell et al., 2012). This supports the need for more efforts to be made on a natural product derived herbicides and makes attractive the prospect of evaluating a vast number of undiscovered or understudied natural compounds that are likely to have biological activity (Evidente et al., 2011; Evidente and Abouzeid, 2006).

Fungal ecofriendly agribiologicals are plant protection molecules gaining momentum for agrichemical research nowadays. Our research group has actively been involved with isolation of phytopathogenic fungi, extraction of phytotoxins, determination of their herbicidal potential, mass production and formulation of these herbicidal metabolites.

IV Fungi as sources of antibiotics

'Antibiotic' term literally means 'against life'. Originally, the term antibiotics canopied only those organic compounds, produced by bacteria and fungi, which were toxic to other microorganisms (Hugo and Russell, 1998). Antibiotics substances produced by natural metabolic processes of some microorganisms that can inhibit or destroy other microorganism (Talaro and Talaro; 2002; Yim et al., 2006). Antibiotics represent the single largest contribution towards drug therapy in health care which has provided effective control of many microbial pathogens in human and animals (Robert et al., 1996; Donadio et al., 2010). A major breakthrough happened in 1940 with the discovery of penicillin, the first, best-known and most widely used antibiotic (Taylor et al., 2003; Sommer 2006) by an English Bacteriologist, late Sir Alexander Fleming from the blue green soil mould *Penicillium notatum*. This discovery marked the beginning of the era for the development of antibacterial compounds from microbes. Streptomycin, another antibiotic, was isolated in 1944 by Waksman, a Microbiologist, from a species of soil bacteria, called *Streptomyces griseus* and has proved to be effective against tuberculosis. After this, rigorous search for more antibiotics lead to the discovery of other antibiotics *viz*., chloromycetin by Burkholder (Cupp, 2004; Sommer, 2006) from *S. venezuelae*. It has a powerful action on a wide range of infectious Gram positive and Gram negative bacteria. The ability to produce antibiotics has been found mainly group Aspergillales of Fungi and in a few other bacteria (Schlegel, 2003). *Streptomycetes* produce an arsenal of antibiotics, exhibiting chemical diversity (Talaro and Talaro, 2003). So far, about 2,000 antibiotics have been characterized but only 50 have been used therapeutically (Schlegel, 2003).

About five thousand antibiotics have been identified from gram-positive, gram-negative bacteria and filamentous fungi but only hundred antibiotics have been commercially available to treat human, animal and plant disease (Bulock and Kristiansen, 1997). Fungal antibiotics find their wide applications in current health care systems especially the penicillin, cephalosporin and fusidic acid, which have antibacterial and antifungal activity (Dobashi et al., 1998). A copious number of antibiotic drugs have been discovered from soil-inhabiting microorganisms which include fungi



(20% of isolated antibiotics), actinomycetes (70%) and eubacteria (10%) (Baltz, 2008; Makut and Owolewa, 2011). At present, the largest producers of microbial metabolites are fungi (45%), which includes basidiomycetes (mushrooms; 11%) and microscopic eukaryotic organisms (33%), such as microscopic, filamentous fungi including *Penicillium*, *Aspergillus* and *Trichoderma* and hundreds of other species (Demain and Sanchez, 2009;Berdy, 2012). These strains represent almost 99% of all fungal metabolites. Other types of fungi, such as yeasts and slime molds, are very poor producers, producing less than 400 products altogether, which is ~1.5% of all metabolites. Henceforth, there is a burgeoning interest during the last few decades for characterizing novel fungi capable of producing natural compounds, as potential source of new antibiotics.

V. Fungal Antibiotics (Source: www. Nature Reviews.com)

Introducing advanced methods for the identification of the hidden microbial biosynthetic machinery to revitalize the discovery of antibiotics is the need of the hour. In addition to the discovery of new natural resources and the search for new and unique environmental surroundings, progress in molecular biology, chemical microbiology, genomics and genetic engineering is essential. In addition, mining genomes and metagenomes for cryptic pathways, combinatorial biosynthesis and the intelligent modification of natural products are important.

Thus, fungi play fundamental and predominant roles in our lives by impacting us in positive and negative ways. They help in generating nutritious food and drink, provide life-saving drugs and are sources of potential enzymes. On the contrary, they adversely affect the structural integrity of our buildings, cause common mycoses and other diseases in humans and animals. The most drastic loss they cause is by affecting the crop plants by causing several diseases, thus threatening global food security.

References

[1] G. Abbas, H., Vesonder, R. F., Boyette, C. D., Hoagland, R. E., & Krick, T. (1992). Production of fumonisins by Fusarium moniliforme cultures isolated from jimsonweed in Mississippi. Journal of Phytopathology, 136(3), 199-203.

[2] Adrio, J. L., & Demain, A. L. (2003). Fungal biotechnology. International Microbiology, 6(3), 191-199.

[3] Barbosa, A. M., Souza, C. G., Dekker, R. F., Fonseca, R. C., & Ferreira, D. T. (2002). Phytotoxin produced by Bipolaris euphorbiae in-vitro is effective against the weed Euphorbia heterophylla. Brazilian Archives of Biology and Technology, 45(2), 233-240.

[4] Baltz, R. H. (2008). Renaissance in antibacterial discovery from actinomycetes. Curr. Opin. Pharmacol. 8, 1–7.

[5] Bérdy, J. (2012). Thoughts and facts about antibiotics: where we are now and where we are heading. The Journal of antibiotics, 65(8), 385-395.

[6] Bulock JD, Kristiansen B. Basic Biotechnology. New York: Academic Press; 1997. p. 433.

[7] Cantrell, C. L., Dayan, F. E., & Duke, S. O. (2012). Natural products as sources for new pesticides. Journal of Natural Products, 75(6), 1231-1242.

[8] Cupp, M.J. (2004). Antibiotics. In Anderson MA, Dede C, Fontana L, Pandkkar KN, Taylor W and Waugh SL (eds), The World Book Encyclopedia Vol. 1, pp 550-552.

[9] Dayan, F. E., Cantrell, C. L., & Duke, S. O. (2009). Natural products in crop protection. Bioorganic & medicinal chemistry, 17(12), 4022-4034.

[10] Dewick, P. M. (2009). The shikimate pathway: aromatic amino acids and phenylpropanoids. Medicinal Natural Products: A Biosynthetic Approach, 3rd Edition, 137-186.

[11] Dobashi, K., Matsuda, N., Hamada, M., Naganawa, H., Takita, T. and Takeuchi, T. (1998). Novel antifungal antibiotics octacosamicins A and B: Taxonomy, fermentation and isolation, physicochemical properties and biological activities. J. Antibiotics. 41: 1525-1532.

[12] Demain, A. L. & Sanchez, S. (2009). Microbial drug discovery: 80 years of progress. J. Antibiot. 62, 5–16.

[13] Donadio, S. et al. (2010). Antibiotic discovery in the twenty-first century: current trends and future perspectives. J. Antibiot. 63, 423–430.

[14] Duke SO (2012) Why have no new herbicide modes of action appeared in recent years? Pest Manag Sci 68:505–512

[15] Evidente, A., & Abouzeid, M. A. (2006). Characterization of phytotoxins from phytopathogenic fungi and their potential use as herbicides in integrated crop management. Handbook of Sustainable Weed Management, 507-532.

[16] Evidente, A., Andolfi, A., & Cimmino, A. (2011). Fungal phytotoxins for control of Cirsium arvense and Sonchus arvensis. Pest Technol, 5, 1-17.

[17] Gaba, S., Perronne, R., Fried, G., Gardarin, A., Bretagnolle, F., Biju-Duval, L., ... & Gibot-Leclerc, S. (2017). Response and effect traits of arable weeds in agro-ecosystems: a review of current knowledge. Weed Research.

[18] Gadermaier G., Hauser M., Ferreira F. (2014). Allergens of weed pollen: an overview on recombinant and natural molecules. Methods 66, 55–66.

[19] Hawksworth, D. L. (1991). The fungal dimension of biodiversity: magnitude, significance, and conservation. Mycological research, 95(6), 641-655.

[20] Harding, D. P., & Raizada, M. N. (2015). Controlling weeds with fungi, bacteria and viruses: a review. Frontiers in plant science, 6, 659.

[21] Hartmann, T. (2007). From waste products to ecochemicals: fifty years research of plant secondary metabolism. Phytochemistry, 68(22), 2831-2846.Hanson JR. Natural products: the secondary metabolites. Royal Society of Chemistry; 2003. ISBN 0854044906.

[22] Hasan, S. and Ayres, P.G. (1990) The control of weeds through fungi: principles and prospects. New Phytologist, 115,201–22.

[23] Hoagland, R. E. (1999) Biochemical interactions of the microbial phytotoxin phosphinothricin and analogs with plants and microbes.--p. 107-125 (No. Colección Reserva Biblioteca/631.8 B615b). En: Biologically active natural products: agrochemicals. Boca Raton, US: CRC Press.

[24] Hoagland, R. E. (2001). The genus Streptomyces: A rich source of novel phytotoxins. Ecology of Desert Environments I Parkash (Ed), 139-169.

[25] Hugo, W.B. and Russell, A.D.,Pharmaceutical Microbiology, 5th edn.Blackwell Science, U K , 1998.

[26] Keller, N. P., Turner, G., & Bennett, J. W. (2005). Fungal secondary metabolism—from biochemistry to genomics. Nature Reviews Microbiology, 3(12), 937-947.

[27] Kuester, A., Conner, J. K., Culley, T., & Baucom, R. S. (2014). How weeds emerge: a taxonomic and trait-based examination using United States data. New Phytologist, 202(3), 1055-1068.

[28] Makut, M., & Owolewa, O. (2011). Antibiotic-producing fungi present in the soil environment of Keffi metropolis, Nasarawa state, Nigeria. eubacteria, 10(18), 19.

[29] Manoharachary, C., Sridhar, K., Singh, R., Adholeya, A., Suryanarayanan, T. S., Rawat, S., & Johri, B. N. (2005). Fungal biodiversity: distribution, conservation and prospecting of fungi from India. CURRENT SCIENCE-BANGALORE-, 89(1), 58.

[30] Mo, X., Li, Q., & Ju, J. (2014). Naturally occurring tetramic acid products: isolation, structure elucidation and biological activity. RSC Advances, 4(92), 50566-50593.

[31] Muller-Scharer, H., Scheepens, P. C., & Greaves, M. P. (2000). Biological control of weeds in European crops: recent achievements and future work. Weed Research-Oxford-, 40(1), 83-98.

[32] Oerke, E. C. (2006). Crop losses to pests. The Journal of Agricultural Science, 144(01), 31-43.

[33] Pandey, A.K. (1998). Herbicidal potential of microorganisms. Present status and future prospects. Pp. 85-105. In: *Microbial Biotechnology for sustainable development and productivity*. Prof. S.K. Hasjia Festschrift vol. 1(ed. R.C.Rajak) Scientific Publishers, Jodhpur.

[34] Pandey, A.K., Jaya Singh, G.M. Shrivastava and R.C. Rajak (2003). Fungi as herbicides: current status and future prospects. In: *Plant Protection A biological approach* (ed. P.C. Trivedi) Aavishkar Publishers, Distributors Jaipur, India. pp 305-339.

[35] Perez-Nadales, E., Nogueira, M. F. A., Baldin, C., Castanheira, S., El Ghalid, M., Grund, E., ... & Naik, V. (2014). Fungal model systems and the elucidation of pathogenicity determinants. Fungal Genetics and Biology, 70, 42-67.

[36] Pusztahelyi, T., Holb, I. J., & Pócsi, I. (2015). Secondary metabolites in fungus-plant interactions. Frontiers in plant science, 6, 573.

[37] Quereshi, S., Khan, N. A., & Pandey, A. K. (2011). Anthraquinone pigment with herbicidal potential from Phoma herbarum FGCC# 54. Chemistry of Natural Compounds, 47(4), 521-523.

[38] Robbert, J.E., Speedie, M.K. and Tyler, V.E. (1996). Antibiotics. In Balado D (ed), Pharmacognosy and Pharmacobiotechnogy. Williams andWilkins, England.

[39] Saxena, S., and Pandey, A. K. (2001). Microbial metabolites as eco-friendly agrochemicals for the next millennium. Applied microbiology and biotechnology, 55(4), 395-403.

[40] Sarbhoy, A. K., Agarwal, D. K. and Varshney, J. L., Fungi of India 1982–1992, CBS Publishers and Distributors, New Delhi, 1996,pp. 350.

[41] Schlegel, H.G., General Microbiology, 7th ed. Cambridge University Press,

[42] Cambridge, 2003.

[43] Talaro, K. and Talaro A. (2002). Foundations in Microbiology, 4th edn. McGraw Hill, New York.

[44] Taylor, D.J., Green, D.P.O. and Stout, G.W. (2003). Biological Science, 3rd edn.Cambridge University Press, Cambridge.

[45] Sommer, C.V. (2006). Antibiotics. In Shapp MG, Gerald FC, Feder B, and Martin LA (eds), The New Book of Knowledge, pp 306-312.

[46] Vikrant, P., Verma, K. K., Rajak, R. C., & Pandey, A. K. (2006). Characterization of a Phytotoxin from Phoma herbarum for Management of Parthenium hysterophorus L. Journal of phytopathology, 154(7-8), 461-468.

[47] Waggoner, B. S., Mueller, T. C., Bond, J. A., & Steckel, L. E. (2011). Control of glyphosate-resistant horseweed (Conyza canadensis) with saflufenacil tank mixtures in no-till cotton. Weed Technology, 25(3), 310-315.

[48] Yim, G., Wang, H. H. & Davies, J. (2006). The truth about antibiotics. Int. J. Med. Microbiol. 296, 163–170