HERBICIDES, BIOTECHNOLOGY

1. Introduction

Biotechnology has provided flew dimensions to herbicide technology. Transgene technolo gy has generated herbicide-resistant crops (1–3), which have had profound effects on the herbicide market. This same technology has the potential to make crops better competitors with weeds through improving competitive traits or making the crop more allelopathic (4–7). Biocontrol agents can sometimes be applied to weeds, much like a herbicide. However, biocontrol has not been widely applied in agronomic and horticultural crops for weed management because of a number of failings when compared to herbicides. However, biotechnological advances may change the equation, favoring biocontrol in some situations. This review will deal with these biotechnology-based methods of weed management. It is an updated version of a pervious review (8).

2. Biocontrol of Weeds with Plant Pathogens

2.1. Current Status. Because of concerns of health, safety, and sustainability, there is a growing interest in reducing chemical weed control measures in both agricultural and natural systems. This has led to an increased interest in the use of biological agents to control weeds. Insects, pathogens, grazing animals, and allelopathic crops can all be used for biological control of weeds. Many of these are listed in the Biological Control of Weeds Handbook (9). There are several advantages of biological control of weeds over chemical or cultural methods. Biological control methods for weeds usually cause less contamination of soil, water, and food with unwanted synthetic compounds, and they do not contribute to soil erosion, as tillage, the main nonchemical method of weed management, does Furthermore, they are generally more targeted to specific weeds than are synthetic herbicides. Potential for movement to nontarget organisms, cost, and limited efficacy have limited the use of this approach. Biocontrol measures are ideal for weeds that escape chemical control, for organic farming, and for weeds that are in areas in which herbicides cannot be used because of environmental sensitivity. Another major concern is evolved herbicide resistance, which now has developed in more than 200 weed biotypes (10,11). These factors, coupled with the banning of many herbicides, more stringent registration and regulations, and the need for nonchemical alternatives in environmentally sensitive areas, have promoted the use of plant pathogen as biological weed control agents.

Historically, there have been two approaches when using an organism to control weeds. The classical or inoculate approach has been used for invasive weeds outside their geographic origin. In some cases, the rapid spread of some plant species, when introduced to new areas is thought to be due to the absence of natural enemies at these sites. Theoretically, introduction of one or more natural enemies into the new geographic area of infestation would bring the weed under control. This method usually entails inoculation of a limited number of

weeds with the biocontrol organism(s), and depends on its spread to the rest of the target weed population. This approach has generally been used in natural habitats (eg, forest or aquatic areas) or agricultural situations in which rapid weed control is not required (eg, rangeland or orchards). An excellent example is the use of the rust fungus *Puccinnia chondrillina* for the control of rush skeletonweed *(Chondrilla junceaea)* in Australia (12). Furthermore, populations of biocontrol organisms are difficult to maintain in annual crops, where the microenvironment and vegetation change dramatically during the growing period. In an annual crop, introduction of the biocontrol agent would usually be required every year. With the classical approach, introduction of the biocontrol organism into a new part of the world poses major risks if there is not absolute target organism specificity.

Spread to nontarget species is not a problem with the other approach, the inundative or augmentative approach. Using this strategy, a native biocontrol organism is provided in sufficient quantity to overwhelm the defenses of the target population of weeds. This strategy is often adequately rapid for use in annual crops. Indigenous biocontrol species are generally used with this approach. Thus, there is generally less environmental risk than with the inoculative approach. The remainder of this chapter will deal only with the augmentative or inundative approach with plant pathogens.

The use of indigenous plant pathogens with limited host specificity in an inundative approach has been the primary emphasis of research and development of microbial herbicides or "bioherbicides". There are several reviews on this topic (eg, 13–17). Several microbes have been patented and commercialized as biocontrol agents for various weeds (9). Table 1 provides a sample of these. Although many have been patented, few of these have been commercialized, and few of those commercialized have remained on the market.

There were two early commercial successes of microbial biocontrol agents: *Colletotrichum gleosoprioides* f.sp. *aeschynomene* (Collego) for management of northern jointvetch [Ae*schynomene virginica* (L.)] in rice and soybeans and

Table 1. **A Sample of Some Commercial Microbial Biocontrol Agents Used for Weed Management**

Microbe	Target weed	Trade name
Alternaria cassiae	*Cassia obtusifolia*	Casst
Alternaria sp.	*Cuscuta* spp.	Smolder
Chondrostereum pupureum	various angiosperm trees	Biochon ECO-clear
Colletotrichum gloeosporioides f.sp. *aeschynomene*	*Aeschynomene virginica*	Collego
Colletotrichum gloeosporioides f. sp. cuscutae	*Cuscuta* spp.	Lubao 2
Colletotrichum gloeosporioides f. sp. malvae	*Malva pusilla*	BioMal
Cylindrobasidium laeve	*Acacia* spp.	Stumpout
Fusarium spp.	*Abutlion throphrasi*	Velgo
Phytophthora palmivora	*Morrenia oderata*	DeVine
Puccinia canaculata	*Cyperus esculentus*	Dr. BioSedge
Xanthomonas campestris pv. *Poannua*	*Poa annua*	XPo, Comperico

Phytopthora palmivora (DeVine) for management of stranglervine [*Morrenia Oderata* (H. & A.)] in citrus orchards. DeVine produces a lethal root rot and can persist saprophytically for extended periods, providing residual control over >1 year. Indeed, this is considered a marketing constraint since only one application may provide weed control over several growing seasons (18). *C. gleosporioides* f.sp. *aeschynomene* produces lethal stem and foliage blight, persisting in dead host shoot and root tissues. However, it must be reapplied in each growing season that is beneficial to the marketer, but not to the consumer.

Both of these organisms can exist as both facultative parasites and saprophytes, giving them sufficient residual activity for adequate efficacy. Their saprophytic nature also allows them to be produced in large quantities on simple media. These bioherbicides will grow over a sufficiently wide range of temperatures and moisture levels improving their use in the field. Furthermore, they are both genetically stable, and their target weed has little or no resistance to them.

Adoption of a weed management product by farmers requires that it be sufficiently economical and efficacious to compete with available alternative methods. Also, the suppliers of the product must make an acceptable profit from that product. Several factors have made these requirements difficult to achieve for microbial herbicides.

Commercial herbicides target many weed species, but most bioherbicides are host specific, targeting only one species or a few closely related species. Unless the target weed species is a major problem [eg, barnyardgrass *(Echinocloa crus-gali* (L.) Beauv] in rice, the biocontrol agent is likely to be too expensive for use with just one weed. The use of broad-spectrum bioherbicides such as *Myrothecium verrucaria* has only recently been considered and shows promise for invasive weeds such as kudzu *(Pueraria lobata)*, a weed that covers millions of hectares in the southeastern United States (19). Although this pathogen infects several plant species (20), the congestive nature of kudzu and the fact that the weed is not usually found in extensive agronomic areas are not considered to be biological or economical constraints.

Host range can be expanded through formulation or genetic alteration. For example, Boyette and Abbas (21) found that the host range of *Alternaria crassa*, a pathogen specific for *Datura stramonium*, could be expanded to include *Sesbania exaltata, Solanum ptycanthum, Crotalaria spectabilis, and Xanthium* spp. by addition of water-soluble filtrates of weeds or fruit pectins to the spore suspensions. Although the host range was also altered to include some solanaceous crops, the pathogen could still be used with these crops if the timing of the applications were carefully considered. Formulation with invert emulsions expanded the host range of *Alternaria cassiae* (22) and *Colletotrichum truncatum* and *C. gloeosporioides* f. sp. *aeschynomone* (13).

Most of the other problems associated with microbial biocontrol agents for weeds can be attributed to efficacy that is unpredictable and/or too poor to be economical. Most of these organisms require a very narrow environmental window compared to most commercial herbicides. Most commonly, they require an extended period of dew or very high humidity in order to infect the host. For example, a 20-h dew period was required for maximal effectiveness of *Colletotrichum coccodes* as a biocontrol agent for *Abutilon theophrasti* (23). Zorner and co-workers (24) concluded unless the dew requirement problem can be economically

solved, commercialization of mycoherbicides such as *A. cassaie* that has an 8-h dew requirement is unfeasible.

Microclimate-related efficacy problems have been solved or reduced with innovative formulations (25). For example, formulation of mycoherbicide spores in invert emulsions provides the proper microclimate, trapping water in the formulation and increasing the time that the spore has to infect target species. With this type of formulation, Quimby and co-workers (26) essentially eliminated the dew requirement for adequate efficacy of *A. cassiae* for control of *Cassia obtusifolia*. Vegetable oil-based formulations also have been shown to improve biocontrol efficacy under moisture-limiting conditions. Emulsions consisting of an emulsifying agent and a vegetable oil reduced the dew period requirement of *Colletotrichum orbiculare* for control of spiny cocklebur *(Xanthium spinosum)* (27). Application of *C. truncatum* in corn oil-surfactant emulsions also reduced the dew period requirement, delayed the need for free moisture, and reduced the spray volume required for effective control of hemp sesbania *(Sesbania exaltata)* (28). Solid formulations, such as granules, pellets, or pasta-like materials (Pesta) that are applied to soil can also overcome dew requirements (25). These materials can become spore-producing systems in the field when moisture levels are adequate for spore germination and mycelial growth. Furthermore, viability can be stabilized in such materials (29).

Wounding the target plant, either mechanically or with a contact herbicide, increases the virulence of most plant pathogens. For example, paraquat applied before the mycoherbicide *Puccinia canaliculata* to *Cyperus esculentus*, resulted in almost complete control of the weed, compared to 10 and 60% control for paraquat and the mycoherbicide, respectively [discussed by Boyette (13)]. The problem in most crop situations is that the wounding must be confined to the weed. Thus, a selective herbicide or selective method of wounding the weeds must be used. Herbicides can improve microbial bioherbicides through other means. Christy and co-workers (30) reported synergy between several herbicides and several fungal plant pathogens. For example, the trimethylsulfonium salt of glyphosate was found to synergize *Xanthomonas campestris* against an array of weed species, presumably due to glyphosate's interference with the weeds' ability to produce phytoalexins derived from the shikimate pathway. An extensive review on the potential of herbicides and other chemicals to improve microbial herbicides is available (31). The wounding approach is ideal for weeds in mowed areas, such as in turf. *X. campestris* pv. *poannua* enters the host through mowing wounds, causing lethal, systemic wilt of the target species (32).

There is less need for dew with plant pathogens that cause soil-borne diseases. Application can be to moist soil or can be made in granules that are activated after rain or irrigation. Deleterious rhizobacteria applied in an inundative fashion have been proposed for control of weeds (33). Deleterious rhizobacteria do not directly kill the weeds, but reduce their growth and competitive ability.

The application technology for foliar application of microbial biocontrol agents can be challenging. For example, ordinary spray equipment will not work with viscous invert emulsions. Spray systems are available for such formulations, but the added cost of the specialized application system reduces the probability of adoption by a farmer. Quimby and Boyette (34) discuss application technology for microbial biocontrol agents in detail.

Finally, the limited shelf life and special storage conditions of a living organism are other complications and expenses that limit adoption of many of these products. In some cases, the product almost has to be produced on demand as is the case with DeVine (18). Research to improve shelf life, so that these materials can be handled more like chemical products, has been conducted (eg, 35,36), but this work is in its infancy.

Agricultural ecosystems are a web of interacting factors, each influencing the other, often in subtle ways, but sometimes having unexpected, profound effects. In most cases, particularly in production agriculture, biological control strategies must coexist with other weed management technologies. Thus, we should strive to predict what these interactions will be and how they can be used to improve the efficacy of biocontrol. For example, we mentioned above that chemical herbicides could sometimes synergize microbial bioherbicides. Herbicides can be used at reduced rates in allelopathic rice, improving the control level of both approaches (37). However, we know very little about such interactions.

Conversely, there are indications that some interactions will be antagonistic to biocontrol approaches. For example, the protoporphyrinogen oxidase-inhibiting herbicides induce host resistance to pathogens at sublethal levels (31). Thus, weeds that are not controlled by these herbicides or those that are exposed to drift from aerial applications may be more difficult to manage with microbial bioherbicdes. Due to the complexity of living organisms, the incorporation of weed biocontrol into integrated pest management systems will perhaps be more challenging than with other weed control technologies.

There are numerous good examples of classical biocontrol of weeds in nonagricultural or rangeland settings, yet the use of biocontrol of weeds in horticultural and agronomic crops using with inundative methods has not progressed much further than the point that it was at 20 years ago. Few biocontrol options exist despite significant research efforts and increasing public pressure to reduce or eliminate dependence on synthetic herbicides. Biotechnological improvements of inundative biocontrol agents may change this situation.

2.2. Biotechnology to Improve Biocontrol Agents. As described above, the interest in using biological control agents to control weeds greatly exceeds the availability of efficacious biological control agents, even though numerous weed pests and pathogen have been identified (14). With weed pathogens, formulation, mass production, and storage life of the pathogens are frequently cited as limitations in their development into commercial products. However, the majority of the described weed pathogens simply lack sufficient virulence or host range to provide economical and efficacious weed control. Without a major effort to genetically modify weed pathogens to modify host range and/or increase virulence, the rate of commercialization of microbial weed biological control agents will probably remain low.

Genetic alterations could be used to either expand the host range of a plant pathogen that infects only one or very few plant species or to reduce the host range of a plant pathogen that attacks almost all plants. One suggested approach is to modify virulent, nonselective plant pathogens such as *Sclerotinia, Phytophthora Pseudomonas*, and *Rhizoctonia* spp. rendering them auxotrophic, ie, dependent on an exogenously supplied micronutrient, or having the auxotrophic

trait under control of a repressor gene that is inactivated in the presence of a chemical specific for the target plant (38–40). For example, *Sclerotinia* sclerotiorum infects a large range of weed species, and mutations that limit its growth without added nutrients could be used to limit its infection to plants that it is sprayed on. Auxotrophic mutants of this pathogen requiring the amino acids arginine or leucine for infection and growth were produced using non biotechnological means. The added amino acid would allow infection of the host, and the pathogen would eventually gain access to the amino acid from the host. Without the amino acid in the application formulation, the pathogen would not infect, thereby insuring that nonsprayed plants would not be infected and that the pathogen would not spread from infected plants to nontarget plants. In the cytosine auxotroph of *S. sclerotiorum*, the host range was reduced in the absence of cytosine in the formulation (41). Thus far, this approach has not been commercially successful, at least partly because auxotrophic strains proved to be less fit in field trial than the wild-type strains.

Another approach is to modify microbial biological control agents with genes for phytotoxin production. A study by Brooker and co-workers (42) demonstrated that the biological activity of the fungal weed biological control agent *C. gloeosporioides* f. ap. *aeschynomene* (Collego) that was previously modified to be resistant to bialaphos (a nonselective, natural herbicide) was enhanced when applied with bialaphos. Attempts to alter the virulence of the plant pathogen *X. campestris* pv. *campestris* by transforming it with genes required for bialaphos production were unsuccessful (43). However, bioassays failed to demonstrate that the *X campestris* transformants actually produced the phytotoxins, and the gene cluster used to transform *X. campestris* may not have contained all the genes required for bialaphos production (44). More recently, strains of *Fusarium oxysporum* Schlechtend.:Fr. and *Fusarium arthrosporiodes* Sherb isolated from *Orobanche aegypticaca* Pers. tissue and *Colletotrichum coccodes* (Wallr) Hughes strain AG-90, specific for *Abutilon theophrasti* Medic. (velvetleaf), were genetically modified to overproduce indole-3-acetic acid (IAA) (45,46). Transformants were capable of producing more IAA than the wild-type stains only if tryptophan was added to the growth media. Similarly, virulence of the *Fusarium* transformants on *Orobanche* plants and *C. cocodes* on velvetleaf was enhanced only if tryptophan was either added to the fungal growth media or when sprayed with tryptohphan. *Colletotrichum coccodes*, transformed with a plasmid containing the *NEP1* gene (a necrosis and ethylene-inducing gene) produced the NEP1 protein and were more virulent on velvetleaf plants in the one to three leaf stage than the wild-type strain (46). However, attempts to produce NEP1 producing *Fusarium* species that attack *Orobanche* failed (47). In a related study, shoot growth reductions of Canada thistle, *Cirsium arvense* L. (Scop.), common ragweed, *Ambrosia artemisiifolia* L., and common dandelion, *Taraxacum officinale* Weber ex Wiggers, caused by applying *P. syringae* pv. *tagetis* and NEP1 were not greater than that caused by *P. syringae* pv. *tagetis* applied alone (48).

While there is interest in developing hypervirulent biocontrol agents, there is concern that the host range of the hypervirulent strain may become altered or the hypervirulent trait could be transferred to other microbial strains associated with nontarget plant species. In some bacteria and fungi, DNA is readily transferred

between species through the process of conjugation. While not enough is known about fungal or bacterial population genetics to allow us to say with certainty that gene exchange can be totally prevented, it may be possible to greatly reduce the likelihood of hypervirulence genes being expressed in undesirable organisms through modifications that limit gene exchange and/or result in the death of strains that receive hypervirulence genes unintentionally. For example, horizontal gene transfer between bacterial species requires the formation of pili, appendages that extend from the cell surface and serve to bring two cells together, and enzymes and proteins involved in the duplication and transfer of the DNA from cell to cell (49). Insertional mutations into specific genes required for pili formation in *Pseudomonas stutzeri* abolished pili formation and natural transformation (50). A mutation in the gene *comP* resulted in a severe defect in the capacity of *Neisseria gonorrhoeae* to take up DNA, but the mutation did not alter pili biogenesis (51). Alternatively, it has been proposed that the hypervirulence transgene be flanked with transgenic mitigator genes that are positive or neutral to the biocontrol agent but would be detrimental to any recombinant (52).

In agricultural situations where the crop is closely related to the target weed, no combination of failsafe measures may be sufficient to allow the release of a microbial weed biological control agent that has transgenic virulence traits. However, in natural areas where the surrounding vegetation has little or no genetic relationship with a persistent, invasive weed, the environmental hazard of not using an efficacious, genetically modified hypoverulent biological control agent may greatly out weigh the risks of deploying one.

3. Control of Weeds with Allelopathy

3.1. Current Status of the Use of Allelopathy for Weed Management.

Plants can interfere with each other through competition for resources or through allelopathy. Although more expansive definitions of allelopathy are used (53,54), for our purposes, allelopathy can be narrowly defined as chemical warfare between different plant species. Both crops and weeds produce phytotoxins that could be allelochemicals that provide an advantage in plant–plant competition. Proving the role of these compounds as allelochemicals has been problematic. The subject of the use of allelopathy to manage weeds has been the subject of books and reviews (eg, 55–59a).

There are several ways that allelopathy could be used in weed management: allelopathic cover or smother crops; allelopathic companion crops; allelopathic mulch or incorporation of phytotoxic crop residues; production of allelopathic crop cultivars with weed-suppressing potential, and use of allelochemicals as sources of natural herbicides. The two later topics are covered in Sections 2.2 and 2.3, respectively.

Cover crops can cause the accumulation of one or more allelochemicals in the rhizosphere. Following cover crop desiccation, the crop of interest is planted through the cover crop residues. Provided the crop is resistant to the accumulated allelochemical(s), which had accumulated in the soil, or were released by degrading cover crop residues, allelochemicals can act to suppress emergence and/or growth of weeds. A recent example is the use of *Sorghum sudanense* as

a cover crop to inhibit weed establishment, followed by no-tillage planting of large-seeded crops such as soybeans that are relatively insensitive to the allelochemicals (59b). This method is effective, but not economically competitive with synthetic herbicides. Research to produce major crops with significant allelopathic properties has thus far not produced a commercial product.

Many others have considered the allelopathic suppression of weeds by various cover crops: buckwheat (60), sorghum (61,62), wheat (63), and rye (64). Fujii and co-workers (65) screened 70 plant species for their ability to poison weeds. In some of these species, L-DOPA (L-3,4-dihidroxyphenylalanine) was mainly responsible for allelopathic activity. Worsham and Blum (66) reported that weeds, such as species of amaranth and common lambsquarter, can be controlled when planted into killed cover crops of rye and subterranean clover. Moreover, soil erosion can be reduced by using surface soil residues of plants. At the same time, residues of cover crops act as a physical barrier for light reaching the soil surface, which may minimize the germination of weeds requiring light for germination.

Rotational crops such as tall red fescue *(Festuca arundinacea)*, creeping red fescue *(F. rubra)*, asparagus, sorghum, alfalfa, black mustard, and oats are used for weed suppression (67). The identification of chemotypes of species with high allelopathic activity and the transfer of such a characteristic into modern crop cultivars could restore a property that might have been inadvertently lost during the process of breeding for higher growth rate and yield. Research with several crops has shown that there is considerable variation in allelopathic activity among accessions, and that some accessions strongly inhibit the growth of certain weed species. For example, Olofsdotter and Navarez (68) screened several rice cultivars fbr allelopathic potential against *Echinocloa crusgalli* (L.) Beauv. in the fields at the International Rice Research Institute. Results showed that 11 cultivars in a dry season and 21 in a wet season had suppressed weed growth (dry matter) by >50%. Laboratory experiments confirmed the field screening results.

3.2. Biotechnology to Improve Allelopathy. As illustrated in the previous section, the available literature on allelopathy is extensive, but its practical use in modern agriculture has been basically limited to the use of cover crops as weed suppressants. Little research has concentrated on the development of allelopathy as an important trait in major agricultural crops, even though it clearly exists in the germplasm of cucumbers (69), barley (70), rice (57,71,72), wheat (73), rye (73), and sorghum (74). At this time, the level of allelopathic activity in these crops is inadequate to provide satisfactory weed management in the field. Standard breeding programs could possibly be used to enhance allelopathy of these crops. However, as long as allelopathy is considered a value added trait of little economic value and yield remains the major selection criteria of most breeding programs, allelopathy will never be developed in cultivars produced by traditional methods. A major reason is that in most cases allelopathy will act as a quantitative trait that is difficult to select for in breeding programs. Furthermore, traditional breeding methods would probably be insufficient for creating lines that provide adequate weed control without the intervention of some application of commercial herbicides. Clearly, partial weed suppression would be a desirable trait in any agricultural setting, but it would be of limited use in modern agricultural practices. Partial control could be very beneficial in

organic farming and countries with limited monetary resources, as it would reduce the amount of hand or mechanical labor needed to remove weeds.

Using breeding methods, imparting this trait to crops that have no allelopathic potential would be impossible. Therefore the fate of allelopathy, as a practical tool for more environmental friendly agriculture, appears to lie in the hands of biotechnology. This task is likely to be more complicated than creating a herbicide-resistant crop or producing a crop with resistance to insects or pathogens, as the applications presently in use are the result of manipulating one gene. The transfer of an allelopathic trait to a non-allelopathic crop may require the manipulation of several genes.

In the few cases where phytotoxic allelochemicals have been identified, there is limited knowledge about their biosynthetic pathways. There are two exceptions: sorgoleone (75) and the benzoxazinones of maize (76). The intensive plant genome programs of rice, arabidopsis, and other plant species will eventually be helpful in providing some of the basic biochemical and genetic information to dissect the biochemical pathways of allelochemicals. While some of the enzymes for the production of secondary metabolites will have similar or the same function as those involved in the production of an allelochemical, some of the enzymes/genes will be species specific and thus will need to be isolated directly from the allelopathic plant.

A traditional approach to identification and isolation of genes encoding enzymes for allelochemical production is to purify the enzymes and work back to the genes (77). The major advantage of such an approach is that when the purification method involves a functional assay, the researcher is fairly confident that the enzyme and gene encoding it are associated with the pathway of interest. The efficiency of this procedure can be enhanced if significant amounts of the specialized tissues can be isolated. This would also be true for procedures where isolation of mRNA is used to isolate the genes of interest.

Expression profiling could be a rapid approach to isolating genes associated with secondary products when these genes are expressed in a defined tissue that can be separated from other tissues. There are several ways to do expression profiling, but there are at least two basic approaches. In the first, messenger ribonucleic acid (mRNA) is isolated from tissues that are and are not expressing the trait of interest. These pools of mRNAs are then compared. In the other approach, an EST (expressed sequence tags) database is created for the tissue/organ where the allelochemical is highly expressed. The database is then mined for genes that are potentially associated with biosynthesis of the allelochemical. The assumption is that genes that are important for the biosynthesis of the compound are manufacturing transcripts at a higher rate in the producing tissue than the nonproducing tissue. This assumption is probably true for the structural genes of a pathway, but this may not be true for a regulatory gene that acts as a suppressor, as its expression might be the reverse of that expected for a structural gene.

The more common methodologies for expression profiling are differential display and subtractive hybridization (78). For each of these procedures, one pool of mRNA is compared with or subtracted from the other pool. Many genes will be expressed at similar levels in both tissues, and these will be removed during the analysis or subtraction procedure. The remaining genes are assumed to represent true differences between the two tissues. These are cloned, identified,

and expression differences are validated. This approach has been used to identify a gene in the biosynthetic pathway of sorgoleone (79).

Gang and co-workers (80) have recently shown that a more brute force method could possibly be used for expression profiling to identify key genes for a given pathway. In this instance, they studied the production of phenylpropenes in the peltate glands of basil. They isolated these glands and the corresponding mRNA within them and found a significant portion of the mRNA to be from genes related to the production of these compounds. A major limitation of this approach is that regulatory genes, which are not highly expressed, might not be identified. A similar approach is being used to isolate the genes for sorgoleone synthesis in *Sorghum* app. root hairs (81).

The ultimate goal of biotechnology research on allelopathy is to either enhance this trait in a crop where this naturally occurs or to transfer this trait to another species. Both of these goals require the production of transgenic plants. A major consideration when producing transgenic plants is to use constructs that are tissue specific in comparison to those that art constitutively expressed. Constitutively expressed promoters can result in autotoxicity or result in unnecessary metabolic costs. In the case of allelopathy, it would be desirable to express the genes solely in the roots or root hairs. To enhance production of allelochemicals in a crop that already has the trait, it would be best to increase the expression of a regulatory gene that is controlling several genes of the biosynthetic pathway. A major consideration when using the EST approach is that regulatory genes, which are not highly expressed, might not be identified.

The genetic enhancement of secondary compounds of crop plants offers potential for enhanced weed management. However, because of the selective nature of allelopathy, it should not be expected that allelopathy alone could control all the weeds in a typical agricultural setting. It could, however, function as a component of the overall weed management strategy. Incorporation of allelopathic traits together with other potential plant interference traits (eg, early vigour, leaf size, plant height and tillering) into commercial cultivars could be a major step toward further development of sustainable crop production systems with less reliance on herbicides.

3.3. Allelochemicals as Herbicide Leads. Rice (54) classified the types of chemical compounds identified as allelopathic agents in 14 categories. We will discuss the allelopathic potential of the more potent allelochemicals that have been shown to be involved in plant–plant interactions. The most important classes are alkaloids, terpenoids, phenolic compounds, and polyacetylenes. In an annual crop, inhibitory allelochemicals must be actively released from the crop into the environment through root exudation, leaching and volatilization, and passively liberated through decomposition of plant residues. Allelochemicals are usually considered to be secondary metabolites of the main metabolic pathway in plants and do not appear to play a role in the basic metabolism of organisms (82).

Many bioassays for allelopathy employ seed germination, seedling growth, or fresh seedling weight to quantify allelopathic effect. Allelochemicals can interfere with cell elongation and cell division. For example, Aliotta and co-workers (83) found that coumarins inhibited cell elongation of the differentiation zone of the root. Abnormal mitotic stages were observed when artemisinin, quassinoids,

lignans, and 1,8-cineole were iested in onion seedling bioassay, suggesting interference with mitosis (84,87). Some compounds can destabilize membranes (88). Inhibition of mineral ion uptake (89,90), respiration and protein synthesis (91), amino acid synthesis (92), and photosynthesis (93) are other important mechanisms of action of allelochemicals.

As discussed above, many of these compounds are cytotoxic and are probably more functional in combating pathogen, insects, and herbivores then in fighting competing plants. For example, several species of *Hypericum* produce the very potent cytotoxin hypericum. In the presence of both light and molecular oxygen, this photodynamic compound is toxic to all living tissues. In the field, under normal circumstances, by the time these compounds reach the soil, their concentration and availability to competing plant species is often too low to influence interference. This is complicated by the fact that soil-bound compounds might be slowly made available to a target plant. Moreover, some compounds are released from the plant in a "benign form" or as "pro-allelochemicals" and need the presence and abundance of the proper microbes to be converted in more potent phytotoxin. An example of this is the conversion of the hydroxamic acid, BOA, by actinomycetes to a much more toxic azoperoxide, AZOB.

Autotoxic activities of phytotoxins have extensively reported and, in general, the more phytotoxic an allelochemical is, the more probable autotoxicity might be. Therefore, one might expect that any level of autotoxicity by allelochemicals could reduce yield of allelopathic crops.

The effectiveness of allelopathic crops and many plant pathogens in killing or suppressing weeds is dependent on natural phytotoxins. At least part of the efficacy of some microbial herbicide preparations has been speculated to be due to the presence of high levels of phytotoxins in the preparation. These compounds could be considered biologically based weed killers. Complete reviews of the topic of natural products for weed management are available (eg, 94–101).

Biocontrol organisms are a potential source of new phytotoxins for consideration in herbicide discovery. Several commercial herbicides, such as the triketones, have been based on natural product structures (102), while others are themselves the natural products. The latter includes pelargonic acid (103), glufosinate (the synthetic version of phosphinothricin) (92), maize gluten (104), and bialaphos (92). Many others, such as AAL-toxin derived from the fungal plant pathogen *Alternaria alternata* (105), have been patented for use as a herbicide, but have not been commercialized. One of the most attractive aspects of natural compounds as herbicides is that they often have entirely new molecular target sites (95,98).

Although natural product-based herbicides have potential for being used directly as herbicides or as templates for new herbicides that might have better toxicological or environmental profiles than synthetic compounds, there is no guarantee of this. For example, AAL-toxin and other highly phytotoxic related compounds have relatively high mammalian toxicity (106). Evolution has sometimes optimized the phytotoxin, but in a form that is commercially impractical. For example, tentoxin, a highly effective phytotoxin from *Alternaria alternata* f. sp. *tenuis*, is too expensive to be used as a commercial herbicide (107). Efforts to discover a cheaper, synthetic analogue of tentoxin with similar herbicidal properties have failed.

Several commercial herbicides have been or will soon be removed from the agrochemical market because of their impact on the environment or the cost of reregistration. Evolution of weed resistance to many commercial herbicides is becoming increasingly problematic because resistance to one herbicide may preclude the use of other classes of chemicals targeting the same site of action. As a result, the number of chemical tools available to manage weeds is becoming limited. Allelochemicals may also be useful in providing leads for synthetic herbicides, as the diversity of molecular structures from living sources provides novels structures that are unlikely to be produced by traditional pesticide synthesis programs. Most biologically active natural compounds are water soluble, nonhalogenated molecules, whereas most synthetic pesticides are lipophilic, halogenated products. Thus, plant-derived secondary compounds may provide a source of environmentally safer herbicides with novel molecular sites of action (98). By modifying these natural products, the end product could be made more active, selective, or persistent. The precursor for the end product may be obtained from a natural source, if the economy of this approach is superior to that of chemical synthesis. An example of a commercial herbicide that contains a natural product moiety is cinmethylin (108). A portion of the molecule is 1,4-cineole, a simple natural monoterpene.

The discovery of triketones, a new important class of herbicides, represents a successful example of the chemical ecology approach used as strategy to select sources of natural products for the discovery of potential herbicides. Following the observation that few plants grew under the bottle brush plant *(Callistemon citrinus)*, triketones, derivatives of naturally occurring phytotoxin leptospermone, were synthesized (102,109). In addition, this new class of herbicides led to the discovery of a new molecular target site *p*-hydroxyphenylpyruvatedioxygenase (HPPD), an enzyme involved in plastoquinone synthesis. Other natural products, such as sorgoleone and usnic acids, are also good inhibitors of HPPD (110). Once a natural product has been found to have good phytochemical activity, it is necessary to consider how this information can be applied. In exceptional cases a compound may perform sufficiently well to be a producti. Generally, the chemical complexity of many secondary products, which often includes multiple chiral centres, prohibits economical production of the compounds, thus the source of the compound then becomes a key issue. Few natural products have all the necessary characteristics to compete with the best synthetic agrochemicals. It is much likely, therefore, that a plant natural product will be used as a lead for synthesis rather than as a product. The toxophore is used as a base for the synthesis of analogues, which will hopefully show improvements over the original compound. Unfortunately, in many cases, desired activity is often lost or greatly diminished when the molecule is simplified. For example, much structure–activity research with the highly phytotoxic cyclic tetrapeptide, tentoxin, has not led to a simple molecule with acceptable activity (111,112). The herbicidal activity of glufosinate (phosphinothricin) is better than that of structural analogues (92). In many cases, improvements *in* both the potency and physical properties are necessary to generate a commercially viable product. However, if the mode of action of the compound is novel, it may provide a source of inspiration to biochemists and result in the development of a new bioassay capable of detecting other, structurally simpler, compounds with the same mode of action.

4. Crop Resistance to Herbicides via Biotechnology

For the past half century, agricultural weed management has been dominated by the use of selective herbicides. In developed countries, herbicides are the dominant class of pesticides. Presently, 70–75% of the pesticides sold (by volume) in the United States are herbicides (113). Genetic engineering has provided alternatives to pesticide use in managing microbial and insect pests in crops (eg, 114,115), but the first transgenic crops designed for better weed management have been those which resist herbicides. This topic has been reviewed in two books (1,116), and is the subject of numerous reviews (eg, 2,3,6, 117–121). Here, a brief review of the area of herbicide-resistant crops (HRCs) produced by biotechnological methods is provided.

4.1. Glyphosate Resistance. Glyphosate is a highly effective, but environmentally and toxicologically safe, herbicide that inhibits a critical enzyme of the shikimate pathway, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). The shikimate pathway produces aromatic amino acids and a large number of secondary products, including lignins, flavonoids, and tannins. EPSPS does not exist in animals. Glyphosate is very mobile within the plant, with preferential transport to metabolic sinks such as meristematic tissues and developing tissues (122). It is relatively slow acting, so that it is transported throughout the plant before growing tissues are killed. For this reason, it is very effective in controlling perennial weeds in which subterranean tissues must be killed in order to prevent regrowth. Although some of the phytotoxicity of glyphosate is a result of reduced pools of aromatic amino acids, most of its the herbicidal effect appears to be caused by a general disruption of metabolic pathways through deregulation of the shikimate pathway (123).

Glyphosate-resistant crops required considerable research and development effort to produce (124). The greatest difficulty in obtaining a crop with sufficient resistance for commercial use was obtaining a glyphosate-resistant form of EPSPS that retained adequate catalytic efficiency to function well in the shikimate pathway. Simply amplifying gene expression of the glyphosate-susceptible form of the enzyme did not provide adequate levels of resistance for field use. Attempts to isolate a microbial gene encoding a C-P lyase that could degrade glyphosate in transgenic plants were unsuccessful. After exhaustive evaluation of both natural and mutant glyphosate-resistant forms of EPSPS, the naturally occurring CP4 EPSPS from *Agrobacterium* sp. strain CP4 was used to produce commercial glyphosate-resistant crops. Later, the gene encoding an enzyme that cleaves the C–N of glyphosate (glyphosate oxidase; *GOX*) was isolated from *Ochrobactrum anthropi* (strain LBAA). The *GOX* gene has been used in combination with *CP4* in commercial glyphosate-resistant canola. Neither the *CP4* nor the *GOX* gene imparts resistance to herbicides other than glyphosate. Thus, these genes are linked exclusively to one herbicide. Recently, a gene encoding an enzyme that weakly *N*-acetylates glyphosate has been greatly improved through directed evolution by DNA shuffling (125). This process improved the efficacy of the enzyme by almost 10,000-fold. Resulting transformant plants were highly resistant to glyphosate.

The rapid adoption of glyphosate-resistant crops is due to several factors. First, this technology greatly simplifies weed management (126). In many

cases, it allows farmers to use only one herbicide, and only apply treatments after the weed problem develops. In those cases in which glyphosate is the only herbicide used, the farmer is less dependent on consultants for specialized recommendations for several herbicides that are sometimes applied at different times. Weed management with glyphosate-resistant crops generally requires less equipment, time, and energy than with selective herbicides. The efficacy of glyphosate in combination with glyphosate-resistant crops is generally very good. In many cases, it fills weed management gaps that existed with available selective herbicide (127). Furthermore, the economics of this approach, even with the "technology fee" added to the cost of the seed, are generally good. Most published economic analyses (eg, 128,129) predict an economic advantage for glyphosate-resistant crops over conventional weed management; but, In a few cases, the economics are the same. The herbicide is no longer under patent protection and is being sold in numerous formulations and as several salts with differing cations. The declining cost of glyphosate due the expiration of its patent favors a continued economic advantage for glyphosate-resistant crop-based weed management.

The efficacy of any pest management strategy is never static, due in large part to pest species shifts and the evolution of resistance to management technologies. There are now three different weed species that have confirmed cases of evolved resistance to glyphosate (130–134). Species that are more naturally resistant to glyphosate are likely to become problems in field situations in which glyphosate is used year after year. For example, in glyphosate-resistant soybeans in Iowa, a more glyphosate-resistant weed, common waterhemp (*Amaranthus rudis* L.), has become a problem where it was not a problem before (135). This and similar problems can be solved by rotating herbicides, mixing herbicides, and/or increasing the application rate of glyphosate.

4.2. Glufosinate Resistance. Glufosinate is a nonselective herbicide, although there is considerable variation in sensitivity to glufosinate between plant species most likely due to differences in the uptake, sensitivity of target enzyme glutamine synthetase (GS), and differences in the level of activity of photorespiration. There are no published cases of evolved resistance to glufosinate or other GS inhibitors. However, a variety of oats with resistance to tabtoxinine-β-lactam, a natural glutamine analogue that inhibits GS, has been reported (136). The resistant variety had both cytoplasmic and plastidic GS with reduced sensitivity to tabtoxinine-β-lactam. While the resistant isoforms of GS remained sensitive to methionine sulfoximine, the effects of glufosinate were not tested. Resistance to glufosinate was developed in microshoot cultures or rice grown in the presence of 2-mg/L glufosinate, glufosinate, and its resistance correlated with elevated levels of GS activity. However, this resistance was not maintained in the R1 generation (137).

Resistance to GS inihibitors through the overexpression of GS has been obtained in cell lines of alfalfa *(Medicago sativa)* and rape *(Brassica napus)* and in regenerated tobacco plants *(Nicotiana tabacum)* (138–140). Although the tobacco plants overexpressing GS treated with glufosinate at 2-kg ha^{-1} grew and set seed, and untreated plants grew normally, it was not reported what effect glufosinate treatments had on yield. Developing crop lines resistant to glufosinate by developing plants that overexpress GS may, however, result in

undesirable traits. For example, a poplar hybird *(Populus tremula* x *P. alba)* that overexpressed GS grew 76% taller than the nontransformed control and *Lotus corniculatus* plants that overexpressed GS showed early signs of senescence (141,142). A complicating factor to developing glufosinate resistant plants using this approach is that it would probably require the overexpression of all isoforms of GS in the plant. The presence of isoforms of GS in plants may also partly account for the absence of the development of resistance to glufosinate occurring in the field, as mutations resulting in glufosinate resistance in all isoforms of GS would have to occur simultaneously.

Several plant species are capable of metabolizing glufosinate to the non-GS inhibitors 4-methoxyphosphinico-2-oxo-butanoic acid, 3-methylphosphinicopropanoic acid, and 4-methylphosphinico-2-hydroxy-butanoic acid. However, the genes involved in these metabolic steps have not been pursued as traits for the development of herbicide-resistant plants because shortly after the herbicidal activity of glufosinate was described, glufosinate-detoxifying genes *bar* and *pat* were isolated and characterized from *Streptomyces hygroscopicus* and *S. viridichromogenes*, respectively (143,144). Both *bar* and *pat* were demonstrated to code for a 21-kDa phosphinothricin acetyltransferase (PAT) that is required for the production of an essential intermediate (*N*-acetyldemethylbialaphos) in the biosynthesis of the tripeptide bialaphos. The PAT proteins encoded by both of these genes are structurally and functionally equivalent (145). Acetylation of the free amine on glufosinate makes the molecule too bulky to fit in the active site of GS (146). This form of protection provides a low level of resistance to glufosinate because the isoforms of GS in the plant remains sensitive to glufosinate. Therefore, when levels of glufosinate applied exceed the detoxification rate of the acetyltransferase, or if the acetyltransferase and GS enzymes are spacially apart, damage from the herbicide can occur. The *bar* and *pat* genes have been widely used in plant engineering, not only as dominant genes for engineering weed control into crop species, but as a selectable marker gene for transformation and as reporter genes in chimeric gene constructs (146). Consequently, many plant species including alfalfa, canola *(Brassica napus)*, carrot *(Daucus carota)*, brocolli *(Brassica oleracea)*, corn (*Zea mays*), cotton (*Gossypium hirsutum*), melon (*Cucumis melo*), lettuce (*Lactuca sativa)*, potato *(Solanum tuberosum)*, rice *(Oryza sativa)*, sugarbeet (*Beta vulgaris)*, sugercane *(Saccharum officinarum)*, tobacco, tomato *(Lycopersicum esculentum)*, and wheat (*Triticum aestivium* L.) have been transformed with these genes (Table 2) (147–151). However, to date ,only glufosinate-resistant maize, canola, rice, and cotton are currently commercially available in the United States (3). No weeds have evolved resistance to glufosinate as of this date, but, in canola, the transgene should readily move to weedy relative, since gene transfer occurs even without the selection pressure of a herbicide (152).

4.3. Bromoxynil Resistance. Bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) is an inhibitor of photosynthesis II of photosynthesis, but it is not a widely used herbicide. A microbe with a nitrilase that rapidly degrades bromoxynil was found in a bromoxynil-contaminated area. The gene encoding this enzyme was isolated and has been used to impart bromoxynil resistance in transgenic crops (153). The gene does not impart resistance to other classes of PS II-inhibiting herbicides, thus linking the transgenic crop to a specific herbicide.

Table 2. **Some of the Crop Plants Transformed with the *bar* or *pat* Gene Conferring Resistance to Glufosinate**

Crop	Species	Reference
Alfalfa	*Medicago sativa*	142
Broccoli	*Brassica oleracea*	142
Canola	*Brassica napus*	142
Carrot	*Daucus carota*	142
Corn	*Zea mays*	145
Cotton	*Gossypium hirsutum*	142
Lettuce	*Lactuca sativa*	142
Melon	*Cucumis melo*	142
Potato	*Solanum tuberosum*	142
Rice	*Oryza sativa*	143
Sugarbeet	*Beta vulgaris*	142
Sugarcane	*Saccharum officinarum*	146
Tobacco	*Nicotiana tabacum*	142
Tomato	*Lycopersicum esculentum*	142
Wheat	*Tritichum aestivium*	144

The first introduced commercial HRC was bromoxynil-resistant cotton. This product has been valuable for specific, but not widespread, weed problems (127). Although bromoxynil-resistant cotton has not had the adoption rate of glyphosate-resistant cotton, it has maintained a use rate of ~7–8% of the cotton acreage in the United States. Bromoxynil-resistant canola became available to Canadian farmers in 2000 and was withdrawn in 2002.

4.4. Sulfonylurea and Imidazolinone Resistance. The sulfonylurea and imidazolinone herbicides are very potent inhibitors of the acetolactate synthase (ALS), a key enzyme of branched chain amino acid synthesis (154). They represent a large segment of the herbicide market. Differential metabolic degradation is the mechanism of selectivity in crops in all cases, and specific sulfonylurea and imidazolinone herbicides have been designed for particular crops. However, certain weed species rapidly evolved resistance at the target site level to these herbicides (154). These weeds with a resistant form of ALS appear to pay little or no metabolic penalty for resistance. Thus, crops could be transformed with a resistant form of ALS to broaden the array of compatible ALS inhibitor herbicides and to reduce the potential for phytotoxicity on the crop.

A number of plant-derived, herbicide-resistant forms of ALS have been used as transgenes in the laboratory (155), and crops transformed with some of these have regulatory approval for field testing in the United States. However, the ALS inhibitor-resistant crops produced by biotechnology that are commercially available have been produced by mutation and traditional breeding.

4.5. Resistance to Other Herbicides. Resistance to a large number of other selective herbicides has been achieved with transgenes (1), but most of these will never be commercially available for economic, environmental, toxicological, or other reasons. However, additional HRCs are being developed. For example, crops made resistant to inhibitors of protoporphyrinogen oxidase (Protox) are being developed by Syngenta (156,157). Protox is a key enzyme in the synthesis of chlorophyll and other porphyrin-based molecules. When inhibited

in vivo, its product rather than its substrate accumulates at high levels through a complex sequence of events (158). At these levels, the enzyme product, protoporphyrin IX, is highly toxic in the presence of light and molecular oxygen, killing photosynthetic plants very quickly through the generation of singlet oxygen. Theoretically, there are several mechanisms by which plants could be genetically engineered to be resistant to Protox inhibitors (159). The mechanism chosen by Syngenta is to introduce a resistant form of Protox. Some development and testing of crops made resistant to HPPD-inhibiting herbicides with transgenes has been conducted (160). As of this writing, the future of these HRCs is unclear.

Regulatory approval for field testing of transgenic crops made resistant to 2,4-D, dalapon, chloroacetanilides, and cyanamide with transgenes has been issued in the United States. Whether any of these products will be commercialized is uncertain.

4.6. The Future of Transgenic, Herbicide-Resistant Crops. To date, there are commercial, transgenic HRCs for three herbicides: bromoxynil, glyphosate, and glufosinate (Table 3). Only three transgenes are used with these products. Biotechnology-derived HRCs through mutant selection are also available.

Table 3. **Regulatory Approval for Growing HRCs Commercially Worldwide as of 2003**[a]

Crop	Herbicide	Country	Year approved*
canola	bromoxynil	Canada	1997
	glufosinate	Canada	1995
		U.S.	1995
	glyphosate	Australia	2003
		Canada	1995
		U.S.	1999
cotton	bromoxynil	U.S.	1994
	glufosinate	U.S.	2003
	glyphosate	Argentina	1999
		Australia	2000
		South Africa	2000
		U.S.	1995
	sulfonylureas	U.S.	1996
flax	sulfonylureas	Canada	1996
		U.S.	1999
maize	glufosinate	Argentina	1998
		Canada	1996
		U.S.	1995
	glyphosate	Argentina	1998
		Canada	1998
		South Africa	2002
		U.S.	1997
rice	glufosinate	U.S.	1999
soybean	glufosinate	Canada	1999
		U.S.	1996

[a]Only the first approval for a particular trait for a particular crop in a country is considered. This information was compiled from the agbios database (161) and previously published by Duke (3).

Companies will not market a product unless there is a clear economic reward. With a HRC, the ideal situation is production of transgenic crops that are resistant only to an excellent, reasonably inexpensive, nonselective herbicide to which there is an economic link. To some extent, this has been the case with glyphosate- and glufosinate-resistant crops. However, the market niche has not been ideal for glufosinate resistance in some crops. We are aware of no other opportunities like these in development.

The future for HRCs that are resistant to selective herbicides is less certain. Selective herbicides already exist for all major crops. Thus, a crop that is genetically engineered to be resistant to yet another selective herbicide must fulfill a weed management need that is unmet, such as those use niches filled by bromoxynil-resistant crops. Most selective herbicides belong to herbicide classes represented by several commercial analogues, and thus most resistance transgenes are likely to provide resistance to all members of the herbicide class. The economics of profiting from a HRC tied to selective herbicides hinges on several factors, including: the cost of producing and developing the transgenic crop; whether or not there are economic links to manufacturers of the members of the herbicide class; and the degree of need for the product. Apparently, this equation has not produced positive results for several HRCs with resistance to selective herbicides.

Lastly, public opinion may play a critical role in the future use of HRCs. In a world economy, if a significant sector of a commodity market rejects tranagenic crops, adoption will be crippled.

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