Transgenic Herbal Medicines

Exploring Potential Harms and Benefits

**Eric Yarnell, ND, RH (AHG),
and Kathy Abascal, BS, JD, RH (AHG)**

Abstract

Food plants are not the only plants being actively genetically engineered. Medicinal plants are also being altered in many ways with genes from other species and even kingdoms for multiple purposes. The examples of *Carica papaya* (papaya), *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng), and *Atropa belladonna* (belladonna) are discussed. In each case, there are potentially positive and potentially negative aspects of the resulting transgenic varieties of these medicinal herbs. Many other medicinal plants are being intensively studied, suggesting that the "genie is out of the bottle," and the coming of transgenic medicinal plants and extracts from them in commerce is likely to be inevitable.

Introduction

The attempt to alter plants by adding genes not normally found in them is an ancient art. However, traditionally, this is accomplished by crossbreeding different strains. This alters plants slowly, using only genes from very closely related subspecies or varieties, and has been well-established as a safe and effective practice over millennia.

In modern times, genes can now be moved between species very rapidly. Rather than being limited to members of the same species, modern techniques can move genes between members of different families, orders, classes, phyla, or even kingdoms. This radical and unprecedented capability has aroused great interest among scientists because of the incredible possibilities, yet has also has raised alarms among environmentalists and many members of the public who are concerned about unforeseen consequences

Currently, efforts are underway to develop transgenic medicinal plants. Most attention has focused on development of transgenic foods, and so, little focus has been put on this other field of inquiry. This article explores some of the published information showing that there are many active attempts to develop transgenic medicinal plants, so that practitioners and consumers can both make informed choices about this area of research and be aware of their potential entry into markets.

Papaya

Some transgenic organisms *may* turn out to be, on balance, beneficial, while others *may* turn out to be detrimental. An example still in flux is transgenic *Carica papaya* (papaya), which was largely held responsible for saving the Hawaiian papaya industry from near-collapse that was attributable to papaya ringspot virus (PRSV) in the 1990s.[1] Various papaya strains that were made to express the coat protein of PRSV showed great resistance to PRSV infection. It is not known if other methods would have worked. Since ~ 1999, the vast majority of Hawaiian papayas sold to markets has been transgenic while the majority of papayas from South America is not. Besides being a food, papaya is also an important tropical medicine active against many intestinal parasites.[2]

As yet, no toxicity to humans has been reported from ingestion of transgenic papaya. There is some concern about allergenicity of the modified papaya[3] although, so far, no clearly documented case of allergy to transgenic papaya, not also seen with nontransgenic papaya, has been documented. One study found no likelihood of increasing the allergenicity of papaya by the means used to make it resistant to PRSV, although this study was conducted by the team that developed the fruit.[4] Proponents may see this as a responsible effort by the research team to make sure that their products are safe; opponents may view it as an attempt to protect their products from criticism by weak science.

Such is the highly polarized world of transgenic plants rendered more polarized by the fact that the patent holders of transgenic plants may, on occasion, limit the publication of

DOI: 10.1089/act.2012.18610 • MARY ANN LIEBERT, INC. • VOL. 18 NO. 6
DECEMBER 2012

negative research.[5] Note that these researchers showed that levels of PRSV coat protein in naturally infected, nontransgenic papayas are much higher than those in noninfected transgenic papayas.

Another study by a team that has developed a different transgenic papaya resistant to two viruses found that it had no effect on markers of allergy in ovalbumin-sensitized mice, but it did increase their production of immunoglobulin M.[6] It was not clear if this was a reaction to the transgenic papaya or a beneficial immunostimulatory reaction. It should be noted, incidentally, that some medicinal plant genes are being incorporated into transgenic foods, which could create allergy problems, such as the introduction of genes from *Allium sativum* (garlic) into rice for the purpose of increasing insect resistance in the rice.[7]

However, even in this case, there are unintended consequences. In what appears to have been an accident, transgenic papaya seeds have been planted unintentionally by organic growers. Transgenic papaya pollen has contaminated nontransgenic fields. Given that new U.S. organic standards, as well as most organic standards around the world, do not allow transgenic organic plants, this leads to harm to the organic papaya industry.[8]

Transgenic papaya also appears to be more susceptible to various fungal diseases (e.g., phytophthora) than *wild-type* papaya. This problem, as well as development of weeds resistant to herbicides sprayed in high amounts on transgenic herbicide-resistant species, may help explain why a recent report concluded that use of transgenic plants actually increases the total amount of herbicides used in agriculture, contrary to the claim that transgenic plants would decrease herbicide use.[9]

Ginseng

Panax ginseng (Asian ginseng) and *P. quinquefolius* (American ginseng) are two of the most widely used and most-revered medicinal plants in the world. Despite, or perhaps because of, their already legendary status as panaceas, and because of their economic importance in Asian and North American countries, much work is being done to develop transgenic versions. Ginseng species are slow-growing and, thus, it is difficult to develop improved crossbreeds by traditional methods; this has been an argument for the need for genetic engineering. The potential benefits (disease-resistant strains with higher levels of desirable medicinal constituents) must be weighed against the potential harms (allergenicity, encouraging herbicide and pesticide resistance, and creating imbalanced levels of medicinal constituents, as well as unanticipated problems) when considering whether such work should continue or not.

A common goal in engineering transgenic plants is to make them able to tolerate herbicides and fungicides better. This allows for more intensive monocropping of herbs, which is efficient and profitable, but creates conditions ripe for epidemic disease. More intensive use of herbicides, pesticides, and chemical fertilizers is the industrial approach to

Table 1. Sampling of Other Research on Transgenic Medicinal Plants

Plant species	Type of manipulation	Reference
Catharanthus roseus (Madagascar periwinkle)	Increased alkaloid synthesis	a
Coptis japonica (goldthread)	Increased berberine synthesis	b
Curcuma longa (turmeric)	Herbicide resistance	c
Eschscholzia californica (California poppy)	Increased alkaloid production	d
Lavandula latifolia (spike lavender)	Increase limonene production	e
Linum usitatissimum (flax)	Increased synthesis of multiple medicinal compounds	f,g
Medicago sativa (alfalfa)	Salt tolerance while growing; greener coloration; many others	h,i
Mentha x piperita (peppermint)	Increased volatile oil production	j
Rauvolfia serpentina (Indian snakeroot)	Increased alkaloid synthesis	a
Salvia spp. (sage)	Increased diterpenoid synthesis; increased tanshinone synthesis	k,l

Note: This is not a comprehensive listing. Many other medicinal plants have been genetically modified, at least experimentally.

[a]Pasquali G, Porto DD, Fett-Neto AG. Metabolic engineering of cell cultures versus whole plant complexity in production of bioactive monoterpene indole alkaloids: Recent progress related to old dilemma. J Biosci Bioeng 2006;101:287–296; [b]Inui T, Kawano N, Shitan N, et al. Improvement of benzylisoquinoline alkaloid productivity by overexpression of 3′-hydroxy-*N*-methylcoclaurine 4′-*O*-methyltransferase in transgenic *Coptis japonica* plants. Biol Pharm Bull 2012;35:650–659; [c]Shirgurkar MV, Naik VB, von Arnold S, et al. An efficient protocol for genetic transformation and shoot regeneration of turmeric (*Curcuma longa* L.) via particle bombardment. Plant Cell Rep 2006;25:112–126; [d]Sato F, Hashimoto T, Hachiya A, et al. Metabolic engineering of plant alkaloid biosynthesis. Proc Natl Acad Sci U S A 2001;98:367–372; [e]Muñoz-Bertomeu J, Ros R, Arrillaga I, Segura J. Expression of spearmint limonene synthase in transgenic spike lavender results in an altered monoterpene composition in developing leaves. Metab Eng 2008;10:166–177; [f]Zuk M, Dyminska L, Kulma A, et al. IR and Raman studies of oil and seedcake extracts from natural and genetically modified flax seeds. Spectrochim Acta A Mol Biomol Spectrosc 2011;78:1080–1089; [g]Zuk M, Kulma A, Dyminska L, et al. Flavonoid engineering of flax potentiate its biotechnological application. BMC Biotechnol 2011;11:10; [h]Guan Q, Takano T, Liu S. Genetic transformation and analysis of rice OsAPx2 gene in *Medicago sativa*. PLoS One 2012;7:e41233; [i]Zhou C, Han L, Pislariu C, et al. From model to crop: Functional analysis of a STAY-GREEN gene in the model legume *Medicago truncatula* and effective use of the gene for alfalfa improvement. Plant Physiol 2011;157:1483–1496. [j]Wildung MR, Croteau RB. Genetic engineering of peppermint for improved essential oil composition and yield. Transgenic Res 2005;14:365–372; [k]Kuźma Ł, Kisiel W, Królicka A, Wysokińska H. Genetic transformation of *Salvia austriaca* by *Agrobacterium rhizogenes* and diterpenoid isolation. Pharmazie 2011;66:904–907; [l]Lee CY, Agrawal DC, Wang CS, et al. T-DNA activation tagging as a tool to isolate *Salvia miltiorrhiza* transgenic lines for higher yields of tanshinones. Planta Med 2008;74:780–786.

Potential Long-Term Problems with Transgenic Herbal Medicines

- Spread of transplanted genes to other organisms (e.g., herbicide tolerance)
- Disruption of critical, but previously unrecognized, pathways in the plants
- Introduction of allergenic proteins
- Promotion of evolution of resistant weeds and insects (for herbal medicines engineered to contain toxins to pests, or those that are tolerant to herbicides/pesticides leading to higher use of these compounds)

Sources: Ref 9; Powell M, Wheatley AO, Omoruyi F, et al. Comparative effects of dietary administered transgenic and conventional papaya on selected intestinal parameters in rat models. Transgenic Res 2010;19:511–518.

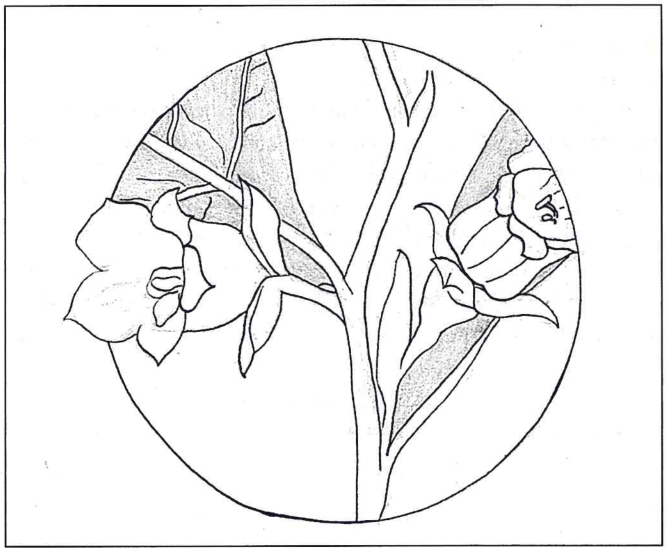
allow such farming practices. However, these chemicals can harm the very plants that are intended for monocropping—hence the need for transgenic plants that can tolerate high levels of toxins.

The bacterial glutamine synthetase–inhibiting herbicide bialaphos is of growing interest for commercial use. A variety of Asian ginseng has been developed in the laboratory that produces an enzyme making it resistant to bialaphos.[10] By adding the gene for phosphinothricin-*N*-acetyltransferase from the bacterium *Streptomyces viridochromogenes*, *P. ginseng* acetylates and inactivates bialaphos, rendering it harmless. This same approach has been implemented with several major staple foods, such as wheat and sugar cane. The long-term effects of this change are unknown (see Potential Long-Term Problems with Transgenic Herbal Medicines).

Another approach seeks to "improve" ginseng by altering synthesis of ginsenosides and other desirable compounds in the plants. Growing *P. quinquefolius* with *Agrobacterium tumefaciens* Ti plasmid results in a transgenic plant that has altered, higher levels of ginsenoside production.[11] Whether this would act the same or be as safe as *wild-type* American ginseng or not is unknown. At least one type of transgenic American ginseng has been shown to contain novel triterpenoid saponins.[12] It is impossible to know at this point if these will prove to be beneficial or harmful in some way.

Two transgenic Asian ginseng lines have been shown to produce an increased level of total ginsenosides compared to the *wild-type*, and both had increased inflammation-modulating effects in vitro.[13] A similar assay system also found transgenic Asian ginseng to be more inflammation-modulating than wild Asian ginseng in vitro.[14]

In vitro, Asian ginseng has also been merged successfully with the human gene for lactoferrin and made to produce 3% by weight of the protein.[15] The idea behind this transgenic plant would be to produce the product in vitro for human consumption, as is now widely practiced using transgenic bacteria. This would seem to be the most benign form of genetic engineering, with no intention of release of the transformed plant into the environment.



Atropa belladonna (belladonna). Drawing © 2012 by Kathy Abascal, BS, JD, RH (AHG).

Belladonna

Work is also being done to alter the chemistry of *Atropa belladonna* (belladonna), an important medicinal plant that is also used as a feedstock to produce alkaloid drugs, such as scopolamine and atropine. As early as 1992, a gene from *Hyoscyamus niger* (henbane) was being inserted into belladonna to increase production of scopolamine.[16] This was primarily to create plants for use as precursors for drugs. Similar efforts have continued to transform belladonna for this purpose.[17]

Transgenic belladonna has also been created by incorporating the mammalian gene for cytochrome P450 2E1. The purpose of this was to serve as a biomarker for other genetic manipulations and possibly as a model for producing other human proteins in vitro from belladonna (similar to the use of transgenic Asian ginseng to make lactoferrin as cited above).[18]

No references could be found on transformation of belladonna for herbicide resistance or improved characteristics for ease of mass cultivation. This could suggest that there is no interest in improved growth of the plant (but instead focusing only on plant callus extracts grown in vitro) and, thus, *wild-types* of belladonna are protected. Only time will tell whether transgenic belladonna will appear in the field.

Conclusion

The level of research on transgenic medicinal plants is impressive and, up to this point, almost entirely hidden from public view. The intense focus on transgenic food crops has perhaps drawn attention away from the wide array of other types of genetic engineering going on. The sheer number of medicinal plants that have already been modified (see Table 1) is sufficiently high that it seems inevitable that transgenic medicinal plants and extracts from them will be brought to markets, if these plants and extracts are not already there.

At present, there are no labeling requirements to prevent the introduction of these plants into general use in the United States, although, presumably, they would have to be approved by the U.S. Food and Drug Administration or the U.S. Department of Agriculture first. However, anything labeled as organic in the United States currently cannot contain transgenic material. It remains to be seen if transgenic herbal medicines will be a boon, a bane, or some mix of the two. ■

References

1. Gonsalves D. Transgenic papaya in Hawaii and beyond. AgBioForum 2004;7:36–40. Online document at www.agbioforum.org/v7n12/v7n12a07-gonsalves.htm Accessed October 1, 2012.

2. Okeniyi JAO, Ogunlesi TA, Oyelami OA, Adeyemi LA. Effectiveness of dried *Carica papaya* seeds against human intestinal parasitosis: A pilot study. J Med Food 2007;10:194–196.

3. Kleter G, Peijnenburg A. Screening of transgenic proteins expressed in transgenic food crops for the presence of short amino acid sequences identical to potential, IgE-binding linear epitopes of allergens. BMC Structural Biol 2002;2:8–19.

4. Fermín G, Keith RC, Suzuki JY, et al. Allergenicity assessment of the papaya ringspot virus coat protein expressed in transgenic rainbow papaya. J Agric Food Chem 2011;59:10006–10012.

5. The Editors. Do seed companies control GM crop research? Scientific American, August 13, 2009. Online document at www.scientificamerican.com/article.cfm?id=do-seed-companies-control-gm-crop-research Accessed October 21, 2012.

6. Chen YN, Hwang WZ, Fang TJ, et al. The impact of transgenic papaya (TPY10-4) fruit supplementation on immune responses in ovalbumin-sensitised mice. J Sci Food Agric 2011;91:539–546.

7. Sengupta S, Chakraborti D, Mondal HA, Das S. Selectable antibiotic resistance marker gene-free transgenic rice harbouring the garlic leaf lectin gene exhibits resistance to sap-sucking planthoppers. Plant Cell Rep 2010;29:261–271.

8. McNarie AD. Plenty Papaya Problems [sic]. *Hawai'i Island J* 2003;March 31. Online document at www.hawaiiseed.org/in-print/press-room/press-clips/plenty-papaya-problems Accessed October 1, 2012.

9. Benbrook CM. Impacts of genetically engineered crops on pesticide use in the US—the first sixteen years. Environ Sci Eur 2012;24:24.

10. Choi YE, Jeong JH, In JK, Yang DC. Production of herbicide-resistant transgenic *Panax ginseng* through the introduction of the phosphinothricin acetyl transferase gene and successful soil transfer. Plant Cell Rep 2003;21:563–568.

11. Song Y, Xu X, Jin Q, Yu R. Cultures of transgenic crown gall from *Panax quinquefolium* and its total ginsenosides content [in Chinese]. Zhong Yao Cai 2005;28:165–167.

12. Zhu JH, Yu RM, Yang L, Li WM. Two new compounds from transgenic *Panax quinquefolium*. Fitoterapia 2010;81:339–342.

13. Choi IY, Kim SJ, Kim MC, et al. Inhibitory effects of the transgenic *Panax ginsengs* on phorbol ester plus A23187-induced IL-6 production and cyclooxygenase-2 via suppression of NF-κB and MAPKs in HMC-1. Immunopharmacol Immunotoxicol 2011;33:205–210.

14. Kim SJ, Jeong HJ, Yi BJ, et al. Transgenic *Panax ginseng* inhibits the production of TNF-alpha, IL-6, and IL-8 as well as COX-2 expression in human mast cells. Am J Chin Med 2007;35:329–339.

15. Kwon SY, Jo SH, Lee OS, et al. Transgenic ginseng cell lines that produce high levels of a human lactoferrin. Planta Med 2003;69:1005–1008.

16. Yun D-J, Hashimoto T, Yamada Y. Metabolic engineering of medicinal plants: Transgenic *Atropa belladonna* with an improved alkaloid composition. Proc Natl Acad Sci U S A 1992;89:11799–11803.

17. Wang X, Chen M, Yang C, et al. Enhancing the scopolamine production in transgenic plants of *Atropa belladonna* by overexpressing *pmt* and *h6h* genes. Physiol Plant 2011;143:309–315.

18. Banerjee S, Shang TQ, Wilson AM, et al. Expression of functional mammalian P450 2E1 in hairy root cultures. Biotechnol Bioeng 2002;77:462–465.

Eric Yarnell, ND, RH (AHG), is chief medical officer of Northwest Naturopathic Urology, in Seattle, Washington, and is a faculty member at Bastyr University in Kenmore, Washington. **Kathy Abascal, BS, JD, RH (AHG),** is executive director of the Botanical Medicine Academy in Vashon, Washington.

To order reprints of this article, e-mail Karen Ballen at: Kballen@liebertpub.com or call (914) 740-2100.