

July 03, 2024

Bernadette Juarez
United States Department of Agriculture
Deputy Administrator, APHIS
Biotechnology Regulatory Services

RECEIVED

By kldiggs for BRS Document Control Officer at 3:24 pm, Jul 03, 2024

Re: RSR number 24-142-01rsr

Dear Ms. Juarez:

With this letter we respectfully request a Regulatory Status Review under 7 CFR part 340 from USDA-APHIS's Biotechnology Regulatory Services for the following Plant Trait Mechanism of Action: *Solanum lycopersicum* (tomato) lines, containing the *Myb12* transcription factor gene from *Arabidopsis thaliana*, engineered for expression in the fruit during ripening, leading to enhanced expression of the phenylpropanoid biosynthesis pathway and increased levels of polyphenolic compounds in the tomato fruit.

This request has been updated and amended to address the information requested in the letter we received June 18, 2024 and a phone call with Dr. Sarah Prewitt on July 1, 2024.

Sincerely yours,

Eric Ward

1. Information about Requestor

Eric Ward
Director
Norfolk Plant Sciences
e.ward@norfolkhealthyproduce.com

2. Does the request contain Confidential Business Information (CBI)?

No.

3. Description of the comparator plant:

Scientific name (genus, species) *Solanum lycopersicum* L.
Common Name: Tomato

4. Genotype of the modified plant.

Sequence of the Insertion:

The inserted sequence contains the *Arabidopsis thaliana* *Myb12* (*AtMyb12*) gene coding sequence, under the control of the tomato E8 promoter. In addition, the insertion contains an NPTII cassette as a selectable marker (Luo et al. 2008). The genetic elements of the transformation construct pSLJ-E8-MYB12 are listed in Table 1. In addition, the complete sequence of the inserted DNA, annotated with each component, is listed in Appendix 1.

5. Description of new trait intended trait

Intended phenotype:

Enhanced levels of polyphenolic antioxidants in tomato fruit. Enhanced levels of anthocyanins in lines containing both the *Del/Ros1* trait and *Myb12* trait. Resistance to aminoglycoside antibiotics (e.g. kanamycin) from the NPTII marker gene.

Description of the MOA:

The NPTII gene product is capable of phosphorylating aminoglycoside antibiotics, including kanamycin, eliminating their antibiotic activity. This gene is commonly used as a selectable marker to identify plantlets that have incorporated the desired gene physically linked to the marker. The phenotype is only useful during the early stages of plant transformation, and has no effect on the plant when no longer exposed to the antibiotic used for selection.

The *AtMyb12* transcription factor gene, when expressed in tomato fruit under the control of the ripening-activated tomato E8 promoter, causes an increase in expression of multiple genes in the phenylpropanoid biosynthesis pathways (Luo et al., 2008). See Figure 1 for a graphical representation of the increases in gene expression in these pathways. The result is accumulation of flavonol derivatives—primarily rutin and kaempferol rutinoside—and caffeoyl quinic acids—mainly caffeoylquinic acid (also known as chlorogenic acid; already the most prevalent soluble phenolic in Solanaceous species), dicaffeoylquinic acid, and tricaffeoylquinic acid (see Figure 2 for a diagram of the pathways and compounds produced).

These elevated enzyme gene expression levels in the fruit, and enhanced levels of various polyphenolic compounds in the fruit, give rise to a yellow or orange color in the fruit (see Figure 3). The *AtMyb12* tomato shows no other phenotype.

In addition, co-expressing *AtMyb12* with the *Del* and *Ros1* transcription factors in the fruit (present in the previously deregulated high anthocyanin Purple Tomato) further increases anthocyanin production in tomato fruit compared to the expression of *Del* and *Ros1* alone, and results in a deep purple “indigo” pigmentation (Zhang *et al.*, 2015) (see Figures 4 and 5). This effect does not appear to be synergistic, but rather additive. Regardless, the effect of adding *AtMyb12* to a *Del/Ros1* tomato line simply intensifies the pigment, and does not result in any other phenotypes.

This combined phenotype would be implemented by crossing an *AtMyb12* line with a *Del/Ros1* line, as described (Zhang *et al.*, 2015).

Table 1. Description of the genetic elements in the transformation construct pSLJ-E8-MYB12 used for Agrobacterium-mediated transformation of tomato..

Genetic element	Donor Organism	Function	Reference
Left T-DNA Border	<i>Agrobacterium tumefaciens</i>	T-DNA boundary	Zambryski <i>et al.</i> , 1982
Vector sequence	synthetic	none-spacer	Luo <i>et al.</i> , 2008
Nopaline synthase promoter	<i>Agrobacterium tumefaciens</i>	Transcriptional promoter	Jones <i>et al.</i> , 1992
Vector sequence	synthetic	none-spacer	Luo <i>et al.</i> , 2008
Neomycin phosphotransferase gene	Bacterial transposon Tn5 (resident in <i>Escherichia coli</i>)	Selectable marker gene conferring resistance to aminoglycoside antibiotics such as kanamycin	van den Elzen <i>et al.</i> , 1985
Vector sequence	synthetic	none-spacer	Luo <i>et al.</i> , 2008
Octopine synthase gene termination region	<i>Agrobacterium tumefaciens</i>	Transcriptional terminator/ polyadenylation signal	Jones <i>et al.</i> , 1992
Vector sequence	synthetic	none-spacer	Luo <i>et al.</i> , 2008
E8 promoter region	<i>Lycopersicum esculentum</i>	Transcriptional promoter activated during fruit ripening	Butelli <i>et al.</i> , 2008
Vector sequence	synthetic	none-spacer	Luo <i>et al.</i> , 2008
Myb12 cDNA coding region	<i>Arabidopsis thaliana</i>	Transcription factor causing increased expression of enzymes in the phenylpropanoid biosynthesis pathway	Luo <i>et al.</i> , 2008
Vector sequence	synthetic	none-spacer	Luo <i>et al.</i> , 2008
Cauliflower mosaic virus termination region	Cauliflower mosaic virus	Transcriptional terminator/ poly-adenylation signal	Hellens <i>et al.</i> , 2000
Vector sequence	synthetic	none-spacer	Luo <i>et al.</i> , 2008
Right T-DNA Border	<i>Agrobacterium tumefaciens</i>	T-DNA boundary	Wang <i>et al.</i> , 1984

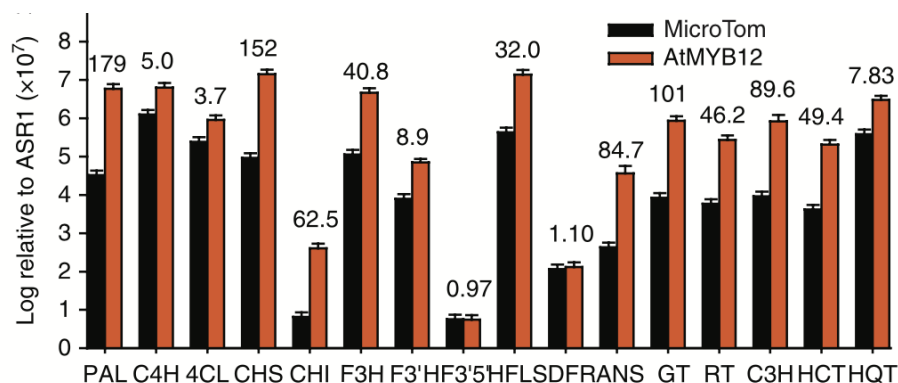


Figure 1. Fold induction of genes encoding enzymes in the phenylpropanoid biosynthesis pathway in *AtMyb12*-expressing tomato fruit. Quantitative RT-PCR determination of transcript abundance for each gene, represented on a log scale relative to the constitutively expressed *ASR1* control gene, used as a reference. MicroTom is the matched control line that was the recipient of the T-DNA containing *AtMyb12*. The fold-increase in expression compared to the MicroTom control is indicated above each bar. PAL, phenylalanine ammonia lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-hydroxy- cinnamoyl CoA ligase; CHS, chalcone synthase; CHI, chalcone isomerase; F3H, flavanone-3-hydroxylase; F3'H, flavonoid-3'-hydroxylase; F3'5'H, flavonoid-3'5'-hydroxylase; FLS, flavonol synthase; DFR, dihydroflavonol reductase; ANS, anthocyanidin synthase; GT, flavonol-3- glucosyltransferase; RT, flavonol-3-glucoside-rhamnosyltransferase; C3H, p-coumaroyl ester 3-hydroxylase; HCT, cinnamoyl CoA shikimate/quinate transferase; HQT, hydroxycinnamoyl CoA quinate transferase. (From Luo *et al.* 2008)

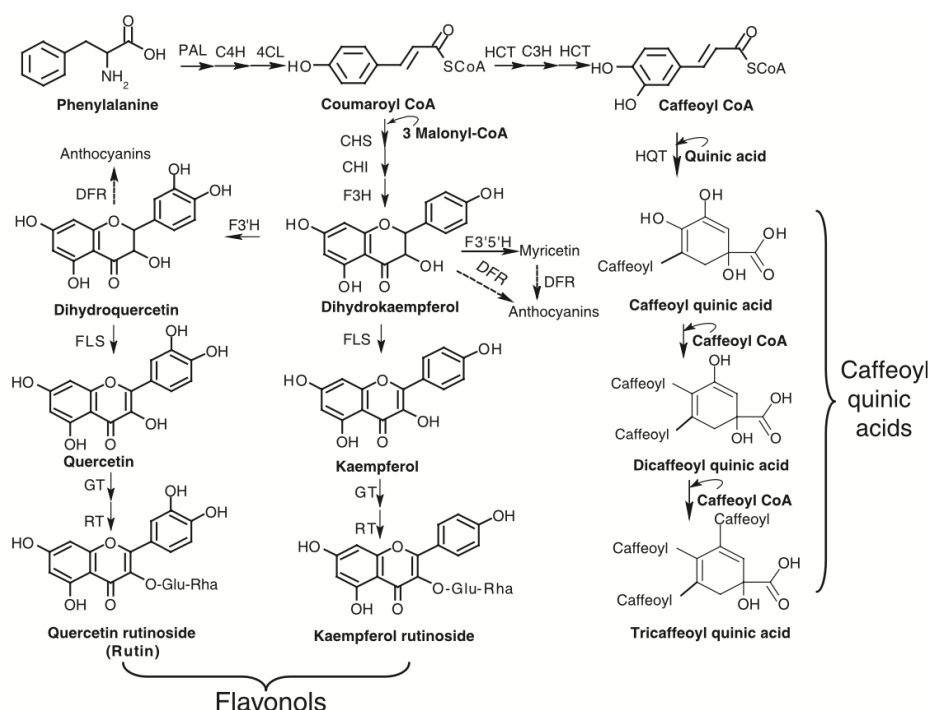


Figure 2. The phenylpropanoid biosynthesis pathway. Enzyme abbreviations are as in Figure 1. (From Luo *et al.*, 2008)



Figure 3. Visible phenotype of the *AtMyb12*-expressing tomatoes. Fruit of wild-type (Money Maker) tomato (top) and a *AtMyb12*-expressing line (bottom). (From Luo *et al.*, 2008)



Figure 4. Visible pigmentation in wild type (WT) tomato compared to fruit expressing the already deregulated high anthocyanin *Del/Ros1* trait, the high flavonol *Myb12* trait, and a combination of both *Del/Ros1* and *Myb12*.

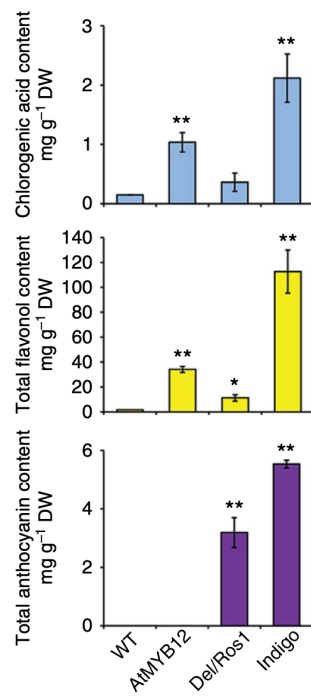


Figure 5. Relative metabolite levels in the same tomato lines depicted in Figure 4.

References

- Butelli, E., Titta, L., Giorgio, M., Mock, H.P., Matros, A., Peterek, S., Schijlen, E.G.W.M., Hall, R.D., Bovy, A.G., Luo, J., and Martin, C. (2008). Enrichment of tomato fruit with health-promoting anthocyanins by expression of select transcription factors. *Nature Biotechnology* 26:1301 – 1308.
- Hellens, R.P., Edwards, E.A., Leyland, N.R., Bean, S. and Mullineaux, P.M. (2000). pGreen: a versatile and flexible binary Ti vector for *Agrobacterium*-mediated plant transformation. *Plant Molecular Biology*, 42:819-832.
- Jones, J.D.G., Shlumukov, L., Carland, F., English, J., Scofield, S.R., Bishop, G.J. and Harrison, K. (1992). Effective vectors for transformation, expression of heterologous genes, and assaying transposon excision in transgenic plants. *Transgenic Res.* 1:285–297.
- Luo et al. 2008. *AtMYB12* regulates caffeoyl quinic acid and flavonol synthesis in tomato: expression in fruit results in very high levels of both types of polyphenol. *Plant J.* 56: 316-326.
- van den Elzen, P., Lee, K.Y., Townsend, J. and Bedbrook, J. (1985). Simple binary vectors for DNA transfer to plant cells. *Plant Molecular Biology*, 5:149-154.
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- Zambryski, P., Depicker, A., Kruger, K., Goodman, H.M. (1982). Tumor induction by *Agrobacterium tumefaciens*: analysis of the boundaries of T-DNA. *J. Mol. Appl. Genet.* 1:361-370.
- Zhang et al. 2015 Multi-level engineering facilitates the production of phenylpropanoid compounds in tomato. *Nature Comms.* 6: 8635. DOI: 10.1038/ncomms9635

Appendix 1. Complete the DNA inserted into the *AtMyb12*-expressing tomato. Nucleotide numbers correspond to the positions in this listed sequence. Compared to the sequence of the vector used for transformation of tomato, the inserted sequence in the tomato genome contains a 688bp deletion from the T-DNA 5' end (including the left border), and a 107bp deletion from the 3' end (including the right border). The corresponding positions in the referenced GenBank accession numbers are easily obtainable with a nucleotide BLASTN¹ search.

1-5 vector spacer sequence; no function

NPTII cassette:

6-166 nopaline synthase promoter (GenBank accessions e.g. CP048576, MN580094.1)

167-233 vector spacer sequence; no function

234-1128 neomycin phosphotransferase II coding sequence (GenBank accession e.g. U00004, MN580094.1)

1129-1154 vector spacer sequence; no function

1155-1862 octopine synthase terminator (GenBank accession numbers e.g. CP119419, MN580094.1)

1863-2902 vector spacer sequence; no function

AtMyb12 expression cassette:

2903-4990 Tomato E8 Promoter (GenBank accessions e.g. KJ561284, MN580094.1)

4991-4996 vector spacer sequence; no function

4997-6112 *AtMyb12* coding sequence (NCBI accession NM_130314.4)

6113-6117 vector spacer sequence; no function

6118-6855 35S terminator (GenBank accession e.g. MN580094.1)

6856-7330 vector spacer sequence; no function

1

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¹ https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastn&BLAST_SPEC=GeoBlast&PAGE_TYPE=BlastSearch

AtMyb12 tomato RSR request (RSR number 24-142-01rsr), updated and amended

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