GENETICALLY MODIFIED PLANTS AND METHODS OF MAKING THE SAME

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/909,074, filed October 1, 2019, which is entirely incorporated herein by reference.

BACKGROUND

[0002] Naturally occurring components in cannabis may impact the efficacy of therapy and any potential side effects. Accordingly, cannabis plants having a modified therapeutic component(s) profile may be useful in the production of cannabis and/or may also be useful in the production of genetically modified cannabis providing a desired drug profile.

SUMMARY

[0002a] In one aspect, provided herein is a transgenic plant that comprises an endonuclease-mediated stably inherited genomic modification of a tetrahydrocannabinol acid synthase (THCAS) gene, the modification resulting in the at least one of the following a-d: a. increased cannabidiol (CBD) in the transgenic plant as compared to a comparable control plant without the modification, b. less than 0.5% by weight of tetrahydrocannabinol (THC) in the transgenic plant as measured by dry weight of the transgenic plant, c. a CBD to THC ratio in the transgenic plant of at least about 25:1, d. reduced or suppressed expression of the THCAS gene in the transgenic plant; wherein the transgenic plant comprises an unmodified endogenous cannabidiolic acid synthase (CBDAS) gene.

[0003] Provided herein is a transgenic plant that comprises an endonuclease-mediated stably inherited genomic modification of a tetrahydrocannabinol acid synthase (THCAS) gene. In some cases, a modification can result in increased cannabidiol (CBD) as compared to a comparable control plant without a modification and wherein the transgenic plant comprises less than 1% of tetrahydrocannabinol (THC) as measured by dry weight. Provided herein is also a transgenic plant comprising an endonuclease mediated genetic modification of a tetrahydrocannabinol acid synthase (THCAS) gene that results in a cannabidiol (CBD) to tetrahydrocannabinol (THC) ratio in the transgenic plant of at least 25: 1 as measured by dry weight. In some cases, a modification reduces or suppresses expression of a THCAS gene.

[0004] In some cases, a transgenic plant described herein comprises a modification that completely reduces or suppresses a CBDAS gene. In some cases, a transgenic plant with increased CBDAS production, comprises an unmodified CBDAS gene. In some cases, a transgenic plant comprises an unmodified endogenous cannabidiolic acid synthase (CBDAS) gene. In some cases, a transgenic plant comprises at least 25% more CBD as measured by dry weight as compared to a comparable control plant without a modification. In some cases, a transgenic plant comprises at least 50% more CBD as measured by dry weight as compared to a comparable control plant without a modification.

[0005] In some instances, a transgenic plant, described herein, contains less than 0.05% of THC as measured by dry weight. In some cases, a transgenic plant comprises a CBD to THC ratio of at least 25:1,

26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 40:1, 45:1, or up to about 50:1 as measured by dry weight. In some cases, a transgenic plant comprises 0% THC or an untraceable amount of THC as measured by dry weight as compared to a comparable control plant without a modification.

[0006] In some cases, a transgenic plant as described herein is modified by use of an endonuclease wherein the endonuclease comprises a clustered regularly interspaced short palindromic repeats (CRISPR) enzyme, transcription activator-like effector (TALE)-Nuclease, transposon-based nuclease, Zinc finger nuclease, argonaute, meganuclease, or Mega-TAL. In some cases, an endonuclease can be a CRISPR enzyme or argonuate enzyme which can complex with a guide polynucleotide. In some cases, a guide

polynucleotide can be a guide RNA or guide DNA. In some cases, a gRNA or gDNA can comprise a sequence that is complementary to a target sequence, or a sequence on a complementary strand to a target sequence in a THCAS gene. In some cases, a guide polynucleotide binds a THCAS gene sequence. In some cases, a CRISPR enzyme complexed with a guide polynucleotide can be introduced into a transgenic plant as a ribonuclear protein (RNP). In some cases, a guide polynucleotide can be chemically modified. In some cases, a CRISPR enzyme and a guide polynucleotide can be introduced into a transgenic plant by a vector comprising a nucleic acid encoding a CRISPR enzyme and a guide polynucleotide. In some cases, a vector can be a binary vector or a Ti plasmid. In some cases, a vector further comprises a selection marker or a reporter. In some cases, an RNP or vector can be introduced into a transgenic plant via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation.

[0007] In some cases, a transgenic plant or cell thereof further comprises a donor polynucleotide. In some cases, a donor polynucleotide comprises homology to sequences flanking a target sequence. In some cases, a donor polynucleotide introduces a stop codon into a THCAS gene. In some cases, a donor polynucleotide comprises a barcode, a reporter, or a selection marker. In some instances, a guide polynucleotide is a single guide RNA (sgRNA). In some cases, a guide polynucleotide can be a chimeric single guide comprising RNA and DNA. In some examples, a target sequence can be at least 18 nucleotides, at least 19 nucleotides, at least 20 nucleotides, at least 21 nucleotides, or at least 22 nucleotides in length. In some cases, a target sequence can be at most 17 nucleotides in length. In some cases, a CRISPR enzyme is Cas9. In some cases, Cas9 recognizes a canonical PAM. In some cases, Cas9 recognizes a non-canonical PAM. In some cases, a guide polynucleotide binds a target sequence from 3-10 nucleotides from a protospacer adjacent motif (PAM). In some cases, a target sequence comprises a sequence complementary to a sequence selected from the group consisting of SEQ ID NOs: 24-34. In some cases, a guide polynucleotide comprises a sequence that comprises at least 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or up to about 100% identity to a sequence selected from the group consisting of SEQ ID NOs 21-34. In some cases, a modification comprises an insertion, a deletion, a substitution, or a frameshift. In some cases, a modification is in a coding region of a THCAS gene. In some cases, a modification can be in a regulatory region of a THCAS gene. In some instances, a plant is a cannabis plant. In some instances, a modification results in up to about 50% of indel formation. In some cases, a modification results in less than or up to about 25%, less than or up to about 15%, less than or up to about 10%, or less than or up to about 1% of indel formation.

[0008] Provided herein is a method for generating a transgenic plant, the method comprising (a) contacting a plant cell comprising a tetrahydrocannabinol acid synthase (THCAS) gene with an endonuclease or a polynucleotide encoding the endonuclease, wherein the endonuclease introduces a stably inherited genomic modification in the THCAS gene; (b) culturing the plant cell with a modification in THCAS gene thereby generating a transgenic plant, wherein the modification results in increased cannabidiol (CBD) as compared to a comparable control plant without the modification and less than 1% of tetrahydrocannabinol (THC) in the transgenic plant as measured by dry weight. Provided herein is also

a method for generating a transgenic plant, the method comprising (a) contacting a plant cell comprising a THCAS gene with an endonuclease or a polynucleotide encoding the endonuclease, wherein the endonuclease introduces a genetic modification in the tetrahydrocannabinol acid synthase (THCAS) gene; (b) culturing the plant cell with a modification in THCAS gene thereby generating a transgenic plant, wherein the modification results in a cannabidiol (CBD) to tetrahydrocannabinol (THC) ratio in the transgenic plant of at least 25: 1 as measured by dry weight. In some cases, contacting can be via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation. In some examples, a method further comprises culturing a plant cell in with a modification in THCAS gene to generate a callus, a cotyledon, a root, a leaf, or a fraction thereof of the transgenic plant. In some cases, a modification reduces or suppresses expression of a THCAS gene. In some cases, a modification does not alter a cannabidiolic acid synthase (CBDAS) gene in a transgenic plant. In some cases, a modification results in at least 25% more CBD measured by dry weight in a transgenic plant as compared to a comparable control plant without a modification. In some examples, a modification results in at least 50% more CBD as measured by dry weight in a transgenic plant as compared to a comparable control plant without a modification. In some examples, a modification results in less than 0.05% of THC in a transgenic plant as measured by dry weight. In some cases, a modification results in a CBD to THC ratio of at least 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 40:1, 45:1, or up to about 50:1 as measured by dry weight. In some instances, a transgenic plant an contain 0% THC or an untraceable amount of THC as measured by dry weight as compared to a comparable control plant without a modification. In some cases, an endonuclease comprises a clustered regularly interspaced short palindromic repeats (CRISPR) enzyme, transcription activator-like effector (TALE)-nuclease, transposon-based nuclease, Zinc finger nuclease, meganuclease, argonaute, or Mega-TAL. In some cases, an endonuclease can be a CRISPR enzyme or argonaute enzyme complexed with a guide polynucleotide that can be complementary to a target sequence in a THCAS gene. In some cases, a CRISPR enzyme complexed with a guide polynucleotide (RNP) or a CRISPR enzyme and a guide polynucleotide can be contacted with a plant cell. In some instances, a guide polynucleotide can be chemically modified. In some instances, a CRISPR enzyme complexed with a guide polynucleotide can be contacted with a plant cell. In other instances, a plant cell is contacted with a vector comprising a nucleic acid encoding a CRISPR enzyme and a guide polynucleotide. In some cases, a vector can be a binary vector or a Ti plasmid. In some cases, a vector further comprises a selection marker or a reporter. In some cases, a method further comprises contacting a plant cell with a donor polynucleotide. In some cases, a donor polynucleotide comprises homology to sequences flanking a target sequence. In some examples, a donor polynucleotide introduces a stop codon into a THCAS gene. In some cases, a donor polynucleotide comprises a barcode, a reporter, or a selection marker. In some cases, a guide polynucleotide can be a single guide RNA (sgRNA). In some cases, a guide polynucleotide can be a chimeric single guide comprising RNA and DNA. In some cases, a target sequence can be at least 18 nucleotides, at least 19 nucleotides, at least 20 nucleotides, at least 21 nucleotides, or at least 22 nucleotides in length. In some cases, a target sequence can be at most 17 nucleotides in length. In some cases, a CRISPR enzyme can be

comprises a sequence that binds a THCAS gene sequence. In some cases, a CRISPR enzyme complexed with a guide polynucleotide forms an RNP and is introduced into a genetically modified cell. In some cases, a guide polynucleotide is a chemically modified. In some cases, a CRISPR enzyme and a guide polynucleotide are introduced into a cell by a vector comprising a nucleic acid encoding a CRISPR enzyme and a guide polynucleotide. In an example, a vector is a binary vector or a Ti plasmid. In an example, a vector further comprises a selection marker or a reporter. In an example, an RNP or vector is introduced into a cell via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation. In an example, a cell further comprises a donor polynucleotide. In some cases, a donor polynucleotide comprises homology to sequences flanking the target sequence. In some cases, a donor polynucleotide introduces a stop codon into the THCAS gene. In some cases, a donor polynucleotide comprises a barcode, a reporter, or a selection marker. In some cases, a guide polynucleotide can be a single guide RNA (sgRNA). In some cases, a guide polynucleotide is a chimeric single guide comprising RNA and DNA. In some cases, a target sequence is at least 18 nucleotides, at least 19 nucleotides, at least 20 nucleotides, at least 21 nucleotides, or at least 22 nucleotides in length. In some cases, a target sequence is at most 17 nucleotides in length. In some cases, a CRISPR enzyme can be a Cas9. In an example, Cas9 recognizes a canonical protospacer adjacent motif (PAM). In an example, Cas9 recognizes a non-canonical PAM. In some cases, a guide polynucleotide binds a target sequence 3-10 nucleotides from PAM. In some cases, a guide polynucleotide hybridizes with a target sequence within the THCAS gene selected from the group consisting of SEQ ID NOs 21-34 or a complementary thereof. In some cases, a guide polynucleotide comprises a sequence that comprises at least 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or up to about 100% identity to a sequence selected from the group consisting of SEQ ID NOs 21-34. In some cases, a modification comprises an insertion, a deletion, a substitution, or a frameshift. In some cases, a modification is in a coding region of the THCAS gene. In some cases, a modification is in a regulatory region of the THCAS gene. In some cases, a modification results in at least or up to about 50% of indel formation. In some cases, a modification results in less than or up to about 25%, less than or up to about 15%, less than or up to about 10%, or less than or up to about 1% of indel formation.

[0010] Provided herein is a tissue comprising the genetically modified cell of any one of the claims 78-119. In an example, a tissue is a cannabis plant tissue. In an example, a tissue is a callus tissue. In an example, a tissue contains less than 1% of THC. In an example, a tissue contains less than 0.05% of THC. In an example, a tissue contains 0% THC or an untraceable amount thereof. In some cases, a tissue comprises at least 25% more CBD measured by dry weight as compared to a comparable control tissue without a modification. In some cases, a tissue comprises at least 50% more CBD measured by dry weight as compared to a comparable control tissue without a modification.

[0011] Provided herein is a plant comprising a tissue. In some cases, a plant comprises at least 25% more CBD measured by dry weight as compared to a comparable control plant without a modification. In some cases, a plant comprises at least 50% more CBD measured by dry weight as compared to a comparable control plant without a modification. In some cases, a plant is a cannabis plant.

[0012] Provided herein is a method for increasing cannabidiol (CBD) production in a plant cell, the method comprising introducing an endonuclease mediated genomic modification into a tetrahydrocannabinol acid synthase (THCAS) gene of the plant cell, thereby minimizing THCAS expression and increasing CBD production of the plant cell as compared to a comparable control cell without the modification. In some cases, a modification reduces or suppresses expression of a THCAS gene. In some cases, a plant comprises an unmodified endogenous CBDAS gene. In some cases, a modification results in at least 25% more CBD in a plant cell as compared to a comparable control cell without a modification. In some cases, a modification results in a CBD to THC ratio of at least 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 40:1, 45:1, or up to about 50:1 in a plant cell. In some cases, a modification results in at least 99% reduction of THC in a plant cell as compared to a comparable control cell without a modification. In some cases, a modification results in at least 99.9% reduction of THC in a plant cell as compared to a comparable control cell without a modification. In an example, an endonuclease comprises a clustered regularly interspaced short palindromic repeats (CRISPR) enzyme, transcription activator-like effector (TALE)-nuclease, transposon-based nuclease, Zinc finger nuclease, argonaute, meganuclease, or Mega-TAL. In an example, an endonuclease is a CRISPR enzyme or argonaute enzyme complexed with a guide polynucleotide that comprises a sequence that binds a target sequence within or adjacent to a THCAS gene. In some cases, a guide polynucleotide binds a portion of a THCAS sequence. In some cases, a guide polynucleotide comprises a sequence that binds a THCAS gene sequence. In some cases, a CRISPR enzyme complexed with a guide polynucleotide forms an RNP that can be introduced into a plant cell. In some cases, a guide polynucleotide is a chemically modified. In some cases, a CRISPR enzyme and a guide polynucleotide are introduced into a plant cell by a vector comprising a nucleic acid encoding a CRISPR enzyme and a guide polynucleotide. In some cases, a vector is a binary vector or a Ti plasmid. In some cases, a vector further comprises a selection marker or a reporter. In an example, an RNP or vector can be introduced into a plant cell via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation. In some cases, a method further comprises introducing a donor polynucleotide into a plant cell. In an example, a donor polynucleotide comprises homology to sequences flanking a target sequence. In some cases, a donor polynucleotide introduces a stop codon into a THCAS gene. In some cases, a donor polynucleotide comprises a barcode, a reporter, or a selection marker. In some cases, a guide polynucleotide is a single guide RNA (sgRNA). In an example, a guide polynucleotide is a chimeric single guide comprising RNA and DNA. In some cases, a target sequence is at least 18 nucleotides, at least 19 nucleotides, at least 20 nucleotides, at least 21 nucleotides, or at least 22 nucleotides in length. In some cases, a target sequence is at most 17 nucleotides in length. In some cases, a CRISPR enzyme can be a Cas9. In some cases, Cas9 recognizes a canonical PAM. In some cases, Cas9 recognizes a non-canonical PAM. In some cases, a guide polynucleotide binds a target sequence from 3-10 nucleotides from a PAM. In some cases, a guide polynucleotide binds a target sequence within a THCAS gene, or binds a sequence complementary to a target sequence within a THCAS gene. In some cases, a guide polynucleotide comprises a sequence comprising from about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or up to about

100% identity to a sequence selected from the group consisting of SEQ ID NOs 21-34. In an example, a modification comprises an insertion, a deletion, a substitution, or a frameshift. In an example, a modification is in a coding region of the THCAS gene. In an example, a modification is in a regulatory region of the THCAS gene. In an example, a plant cell is a cannabis plant cell. In some cases, a method further comprises culturing a plant cell to generate a plant tissue. In some cases, a method further comprises culturing a plant tissue to generate a plant. In some cases, a plant contains less than 0.01% of THC measured by dry weight. In some cases, a plant comprises a ratio of CBD to THC of at least 25:1 measured by dry weight. In some cases, a plant comprises at least 25% more CBD measured by dry weight as compared to a comparable control plant without a modification. In some cases, a modification results in at least or up to about 50% of indel formation. In an example, a modification results in less than or up to about 25%, less than or up to about 15%, less than or up to about 10%, or less than or up to about 1% of indel formation.

[0013] Provided herein is a composition comprising an endonuclease or a polynucleotide encoding an endonuclease, wherein an endonuclease preferentially binds a tetrahydrocannabinol acid synthase (THCAS) gene over a cannabidiolic acid synthase (CBDAS) gene and is capable of introducing a modification into a THCAS gene, wherein a modification reduces or abrogates expression of a THCAS gene. In some cases, a modification reduces or suppresses expression of the THCAS gene. In an example, a modification comprises an insertion, a deletion, a substitution, or a frameshift. In an example, a modification is in a coding region of the THCAS gene. In some cases, a modification is in a regulatory region of the THCAS gene. In some cases, an endonuclease comprises a clustered regularly interspaced short palindromic repeats (CRISPR) enzyme, transcription activator-like effector (TALE)-nuclease, transposon-based nuclease, Zinc finger nuclease, argonaute, meganuclease, or Mega-TAL. In some cases, an endonuclease is a CRISPR enzyme or argonaute enzyme complexed with a guide polynucleotide that comprises a sequence that binds a target sequence within or adjacent to a THCAS gene. In some cases, a guide polynucleotide binds a portion of a THCAS sequence. In some cases, a guide polynucleotide comprises less than 50% identity to a CBDAS gene. In some cases, a CRISPR enzyme complexed with a guide polynucleotide forms a ribonuclear protein (RNP). In some cases, a guide polynucleotide are encoded by a vector. A vector can be a binary vector or a Ti plasmid. In some instances, a vector further comprises a selection marker or a reporter. In some instances, an RNP or vector can be introduced into a plant cell provided herein via electroporation, agrobacterium mediated transformation, biolistic particle bombardment, or protoplast transformation. In some cases, composition provided herein further comprises a donor polynucleotide. In some cases, a donor polynucleotide comprises homology to sequences flanking the target sequence. In some cases, a donor polynucleotide introduces a stop codon into a THCAS gene. In some cases, a donor polynucleotide comprises a barcode, a reporter, or a selection marker. In some cases, a guide polynucleotide is a single guide RNA (sgRNA). In some cases, a guide polynucleotide is a chimeric single guide comprising RNA and DNA. In some cases, a target sequence is at least 18 nucleotides, at least 19 nucleotides, at least 20 nucleotides, at least 21 nucleotides, or at least 22 nucleotides in length. In some cases, a target sequence is at most 17 nucleotides in length. In an example, a

CRISPR enzyme can be Cas9. In some cases, Cas9 recognizes a canonical PAM. In some cases, Cas9 recognizes a non-canonical PAM. In some cases, a guide polynucleotide binds a target sequence from 3-10 nucleotides from a PAM. A target sequence can comprise a sequence complementary to a sequence selected from the group consisting of SEQ ID NOs 21-34. In some cases, a guide polynucleotide comprises a sequence comprising from about 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or up to about 100% identity to a sequence selected from the group consisting of SEQ ID NOs 21-34. In some cases, a modification comprises an insertion, a deletion, a substitution, or a frameshift. In some cases, a modification is in a coding region of the THCAS gene. In some cases, a modification is in a regulatory region of the THCAS gene.

[0014] Provided herein is a kit for genome editing comprising a composition provided herein.

[0015] Provided herein is a cell comprising a composition provided herein. A cell can be a plant cell, an agrobacterium cell, a E. coli cell, or a yeast cell. In some cases, a cell is a plant cell. In some cases, a cell is a cannabis plant cell. In some cases, a cell is a callus cell, a protoplast, an embryonic cell, a leaf cell, a seed cell, a stem cell, or a root cell.

[0016] Provided herein is a plant comprising a cell provided herein.

[0017] Provided herein is a pharmaceutical composition comprising a transgenic plant or a derivative or extract thereof. Also provided herein is a genetically modified cell and/or a tissue. In some cases, a pharmaceutical composition further comprises a pharmaceutically acceptable excipient, diluent, or carrier. A pharmaceutically acceptable excipient can be a lipid.

[0018] Provided herein is a nutraceutical composition comprising a transgenic plant or a derivative or extract thereof. Provided herein is also a nutraceutical composition comprising a genetically modified cell or a tissue.

[0019] Provided herein is a food supplement comprising a transgenic plant or a derivative or extract thereof. Provided herein is also a genetically modified cell or a tissue. In some examples a nutraceutical composition or a food supplement can be in an oral form, a transdermal form, an oil formulation, an edible food, or a food substrate, an aqueous dispersion, an emulsion, a solution, a suspension, an elixir, a gel, a syrup, an aerosol, a mist, a powder, a tablet, a lozenge, a gel, a lotion, a paste, a formulated stick, a balm, a cream, or an ointment.

[0020] Provided herein is a method of treating a disease or condition comprising administering a pharmaceutical composition, a nutraceutical composition, or a food supplement to a subject in need thereof. In some cases, a disease or condition is selected from the group consisting of anorexia, emesis, pain, inflammation, multiple sclerosis, Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease, epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, and obesity.

CLAIMS

WHAT IS CLAIMED IS:

1. A transgenic plant that comprises an endonuclease-mediated stably inherited genomic modification of a tetrahydrocannabinol acid synthase (THCAS) gene, the modification resulting in the at least one of the following a-d:
    a. increased cannabidiol (CBD) in the transgenic plant as compared to a comparable control plant without the modification,
    b. less than 0.5% by weight of tetrahydrocannabinol (THC) in the transgenic plant as measured by dry weight of the transgenic plant,
    c. a CBD to THC ratio in the transgenic plant of at least about 25:1,
    d. reduced or suppressed expression of the THCAS gene in the transgenic plant;

wherein the transgenic plant comprises an unmodified endogenous cannabidiolic acid synthase (CBDAS) gene.

2. The transgenic plant of claim 1, comprising at least 25%, or at least 50% more CBD as measured by dry weight of the transgenic plant as compared to an amount of CBD as measured by dry weight of a comparable control plant without the endonuclease-mediated stably inherited genomic modification of the THCAS gene.

3. The transgenic plant of claim 1, comprising a CBD to THC ratio of at least about: 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 40:1, 45:1; or up to about 50:1.

4. The transgenic plant of claim 1, containing 0% THC or an untraceable amount thereof as measured by dry weight of the transgenic plant.

5. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of a tetrahydrocannabinol acid synthase (THCAS) gene comprises an endonuclease wherein the endonuclease comprises a clustered regularly interspaced short palindromic repeats (CRISPR) enzyme.

6. The transgenic plant of claim 5, wherein the endonuclease comprises Cas9.

7. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene comprises an insertion.

8. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene comprises a deletion.

9. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene comprises a substitution.

10. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene comprises a frame shift.

11. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene is in a coding region of the THCAS gene.

12. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene is in a regulatory region of the THCAS gene.

13. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene comprises an introduced stop codon.

14. The transgenic plant of claim 1, that is a cannabis plant.

15. The transgenic plant of claim 1, further comprising a barcode.

16. The transgenic plant of claim 1, further comprising a reporter.

17. The transgenic plant of claim 1, further comprising a selection marker.

18. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in a.

19. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in a and b.

20. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in a, b, and c.

21. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in a, b, c, and d.

22. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in a and c.

23. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in a and d.

24. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in a, c and d.

25. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in c and d.

26. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in b and c.

27. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in b and d.

28. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene modification results in b, c and d.

29. The transgenic plant of claim 1, wherein the endonuclease-mediated stably inherited genomic modification of the THCAS gene results in d.

30. The transgenic plant of claim 1, which has increased cannabidiolic acid (CBDA) in the transgenic plant relative to a comparable control plant without the endonuclease-mediated stably inherited genomic modification of the THCAS gene.